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THE CLINICAL BEHAVIOR AND MANAGEMENT OF PRIMARY MALIGNANT LYMPHOMA OF THE STOMACH

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PRIMARY lymphomas probably represent less than 3 per cent of all malignant tumors originating in the stomach. Naturally a series from any one center is small, and to fill out the picture it has been the custom to discuss all types of gastric lymphoma together, regardless of whether the involvement of the stomach was primary or not. Most series include both localized disease and cases in which the stomach was involved as part of generalized lymphosarcoma, reticulum cell sarcoma, or Hodgkin's disease. Unfortunately, this type of dilution has served to obscure both the clinical setting and the basis for rational treatment of the primary type of lymphoma. It is rarely made clear how greatly primary and secondary gastric lymphomas differ and especially how much success adequate treatment of the primary form can achieve.

Numerically, secondary gastric lymphomas are more important than are primary. When autopsies from this center were reviewed, involvement of the stomach was found in 42 per cent of 98 cases of lymphocytic lymphoma, in 40 per cent of 121 instances of reticulum cell sarcoma, in 13 per cent of 217 cases of Hodgkin's disease, and in 15.6 per cent of 122 cases of lymphatic leukemia. These 137 examples of secondary gastric lymphoma were collected over a shorter time than it took to collect the 36 examples of primary gastric lymphoma that form the core of this report. However, this type of counting does not reflect the real relative significance of the two types. Secondary gastric involvement in most cases becomes clinically apparent late in the disease, if it is diagnosed antemortem at all.[1] It rarely poses a surgical problem and is never curable by any means. By contrast, the most important fact about primary gastric lymphoma is that it is a lesion potentially curable by surgical or radiation treatment. Many cases

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mimic gastric carcinoma so closely both clinically and anatomically that the first suggestion of their true nature usually comes from the pathologist when he reviews the microscopic slides. These cases not only receive definitive surgical treatment because they are thought to be carcinomas but such treatment actually may be expected to be more effective than for a gastric carcinoma of the same size and stage.[3]

MATERIALS

In line with our policy of including for discussion only those cases which demonstrated an apparent primary lesion in the stomach with metastatic disease confined to the perigastric region, we selected 36 cases observed in the years 1935 to 1956. All had undergone laparotomy with a view to curative surgery which was performed in 31 of 36 patients, a curative resectability rate (86.1 per cent) which is more than twice that for carcinoma (35 per cent). It is possible that the inclusion of 5 nonresectable cases weakens the case for true gastric origin. Unfortunately we have no histologic criteria which enable us to find lymphoma in situ and thereby prove primary origin as we can for carcinoma of the cervix or tongue. Hence, while we feel these nonresectable cases do represent examples of late primary gastric lymphoma, we will identify them separately in our analyses. We are therefore left with 31 cases which meet the strictest practical test we can devise for primacy: disease presenting in such a way that, at operation, it appeared to be encompassable by standard gastrectomy.

THE CLINICAL PRESENTATION OF PRIMARY GASTRIC LYMPHOMA

Age and Sex.—The age distribution of our patients is given in Table I. While the average age is somewhat below that found for gastric carcinoma, it will be noted that most of the cases occur in the fifth, sixth, and seventh decades

TABLE I. AGE AND SEX DISTRIBUTION IN 34 PATIENTS WITH PRIMARY MALIGNANT GASTRIC LYMPHOMA 1935-1955

DECADE	MALES	FEMALES
Total	22	12
20-29		2
30-39		1
40-49	4	2
50-59	8	2
60-69	9	5
70-79	1	

when carcinoma is also most likely to be encountered. There were 22 men and 14 women in the series of operable cases. This 5 to 3 ratio may be compared with a ratio for gastric carcinoma that represents a 2 to 1 or even greater predominance of male over female susceptibility to this disease. It may be coincidence that all 3 patients under 40 were women. The nonresectable group (3 men and 2 women) were all in their 50's and 60's. By contrast, for secondary lymphomas of the stomach, the age distribution was the same as observed in patients with generalized lymphoma, with greater frequency in the younger age groups and almost a 1 to 1 sex ratio.

Diagnosis and Physical Findings.—Symptoms had existed in these patients for an average of 8 months prior to the initiation of definitive treatment. The longest duration prior to treatment was 3 years and the shortest 1 day. Because the gastric orifices were affected only infrequently, vomiting and dysphagia were not predominant symptoms. The most common single clinical picture was that suggestive of peptic ulcer. Twelve of the patients had a classical ulcer symptomatology. A number had responded to medical therapy for some time; one patient was relieved of his symptoms for 2 years. Numerous authors have commented on this observation without attempting to offer an explanation. We are struck by the fact that every one of the cases in our series demonstrated ulceration of the stomach at the time of operation. In many instances a classical crater was present. An example of this type of setting is seen in the history of Patient F. S.:

This 45-year-old man was first examined in October, 1947, because of epigastric pain of 3 months' duration. The pain was completely relieved by drinking milk and by an antiulcer regimen. The patient still remained concerned about weight loss, however; when seen he had lost 25 pounds in this short time. X-rays demonstrated a neoplasm in the distal third of the stomach, "probably carcinoma." At operation two tumors were encountered on the anterior wall of the distal gastric segment. Subtotal gastrectomy was performed. Because of a histologic diagnosis of reticulum cell sarcoma with metastases to lymph nodes, postoperative high voltage x-ray therapy was administered to the operative site in full therapeutic dosage. The patient is living and well in 1959, 12 years later.

This striking and acute weight loss, averaging 25 pounds, was seen in 9 patients and is worth noting as a characteristic of primary gastric lymphomas. In only 2 patients were there palpable abdominal masses. In the remaining cases the symptoms were less distinctive and generally the same as in patients with gastric carcinoma. Hematemesis was described in only 2 of our cases although it has been mentioned by other authors as a frequent symptom. Undoubtedly melena must have been relatively constant, since anemia of the iron-deficiency type was observed frequently. The presence of occult blood in the stool was of no great diagnostic significance, however, since it can be expected in most surgical disorders of the stomach.

Neither gastroscopy nor histologic study of the gastric aspirate gave us any information leading to a diagnosis of lymphoma prior to surgery in the few cases in which they were employed.

X-RAY DIAGNOSIS (ROBERT S. SHERMAN, M.D.)

The diagnosis of primary lymphoma is infrequently established as a result of gastrointestinal x-ray examination. Reports from the literature, as well as our own experience suggest that, in approximately 10 per cent of patients surgically explored, study of biopsy material confirms the radiographic impression of lymphoma of the stomach. Though lymphomas possess most of the morphologic characteristics which usually make them indistinguishable from gastric carcinoma, a few demonstrated features of special interest.

Infiltrating Form.—Thirty-three per cent presented an infiltrative lesion. Usually the infiltration was of the deep variety, producing a rigid narrowing. Sometimes this stenosis occurred at the pylorus and provided an annular defect. Usually, however, it was larger, more irregular, and in almost all instances looked exactly like infiltrating carcinoma. One of the more extensive of the infiltrative lymphosarcomas involved the upper half of the stomach and a 3 inch segment of the adjacent esophagus. It appeared, therefore, exactly like a deeply infiltrating or "scirrhus" carcinoma. The conclusion was quite evident that the infiltrating type of lymphosarcoma was usually indistinguishable from infiltrating gastric carcinoma on the basis of the roentgenologic examination. (Fig. 1.)

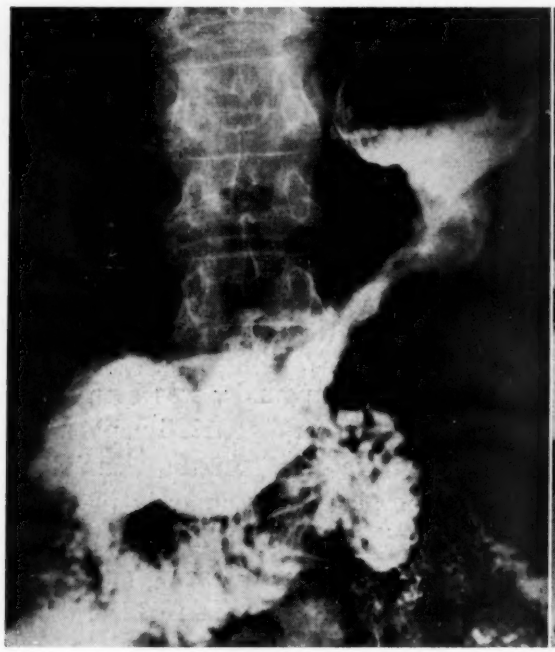

Fig. 1.

Fig. 2.

Fig. 1.—Infiltrating form of gastric lymphosarcoma prior to x-ray therapy.
Fig. 2.—X-ray film of the same stomach 3 months after completion of high-voltage roentgen therapy.

Ulcerating Form.—About 27 per cent of the primary lymphosarcomas examined were ulcerative. Only one of these was located on the greater curvature. The ulcerations were quite varied in size with some having more irregular infiltration about them than others. No example of the meniscus sign was found. While some of these lesions seemed quite characteristically cancerous ulcerations, there was nothing in their morphology to indicate they were specifically lymphosarcomatous. A few showed the common peptic configuration, thereby giving no real clue to their malignant nature. Once again the conclusion was apparent that ulcerating lymphosarcoma presents no distinguishing feature from peptic ulceration at times.

Polypoid Form.—Twenty-seven per cent were polypoid lesions, but the significant point seemed to be that there was always some accompanying infiltration. The roentgen appearance again was that commonly seen in cases of gastric carcinoma. The margins seemed no smoother nor the masses no more circumscribed or lobulated than can be found with adenocarcinoma of the stomach. One salient point turned up, however, in that there was no example of a small circumscribed polyp-like defect. This fact is further supported by our study of the material on small polypoid lesions of the stomach which contained no example of lymphosarcoma.

Special Form.—Approximately 10 per cent of the primary gastric lymphosarcomas presented a special morphologic pattern that seems to be highly useful as an aid in roentgen diagnosis of this disease. This is typified by a generalized involvement of the stomach with a ragged appearance of convolutional folds. There is little or no deep infiltration and the contour and capacity of the stomach are almost unaffected. The disease does not cross the pylorus or invade the esophagus. The folds seem enlarged, more tortuous and irregular than normal and they appear relatively fixed. The normally smooth, regular appearance of the lining of the stomach is lost. Some of the large, irregular, rigid folds give the appearance of isolated or simple polypoid masses, somewhat resembling gastric polyposis except that they possess a long oval rather than spherical shape. Gastric carcinoma in our experience does not seem to produce this particular pattern.

GROSS PATHOLOGIC FINDINGS

While all anatomic divisions of the stomach may be invaded, there was a tendency in our series for the tumors to involve the middle third relatively more often than the other segments (14 cases). Possibly the most distinctive feature in localization was the relative predilection for origin in the anterior or posterior walls (11 cases), rather than the curvatures. In 10 patients the entire stomach seemed involved by the neoplasm. Grossly, the tumor appeared to be primarily submucosal in 43 per cent, involving all layers in 37 per cent, and subserosal in 20 per cent. This latter finding especially seems more suggestive of sarcoma than primary carcinoma.

SIZE OF TUMOR

In 25 cases we have accurate measurements of the sizes of the lesions. The tumors tended to be large. Seventeen were greater than 8 cm. in diameter, 8 measured between 4 and 8 cm., and only 4 were under 4 cm. In addition, as will be described below, microscopic examination usually showed extension beyond the grossly identifiable tumor. It would appear that, in the stomach, size of tumor is a less important factor in survival than the type of tumor. Long-term survival not infrequently follows resection of gastric cancers over 8 cm. in size, a rare occurrence for cancers of other organs. In our series of gastric lymphomas, all of the patients who survived 5 years or more had tumors between 8 and 10 cm. in diameter. (Several patients with low grade adenocarcinomas of the stomach of this size also have been 5-year survivors.)

Ulceration was demonstrated on close inspection in every primary lymphoma. Multiple tumors were noted grossly in 5 instances and, as is described under the microscopic findings, complete examination showed multiplicity to be the rule rather than the exception. Involvement of the liver by direct invasion was a major block to resection. Direct extension from the stomach into adjacent structures was fairly common (13 of 36 cases), apparently more so than in carcinoma. This tendency serves to explain why it was so often necessary to perform extended total gastrectomy when resection was feasible.

MICROSCOPIC PATHOLOGY

One of the problems in organizing the results of our observations was the classification of our material according to cell type. In most series, malignant lymphomas have been subdivided into 3 classes: lymphocytic lymphomas, reticulum cell sarcomas, and Hodgkin's disease, though sometimes under other names. In our material, no case of gastric Hodgkin's disease met our definition of a primary tumor. In keeping with this concept we observed that almost all of the cases of Hodgkin's disease reported in other series of primary gastric lymphomas likewise were disseminated when first seen. Under the microscope, many gastric lymphomas of other types suggest Hodgkin's disease at first glance because they were heavily infiltrated with eosinophils. This infiltration is characterisitic of the stomach itself and not of the tumors. Eosinophils are associated, often prominently, with all types of gastric lymphatic tissue. They will be found in normal cell collections between gastric glands and in the follicles in chronic gastritis, as well as in lymphomas. Hence their presence in gastric lymyphomas means little and the tumors must be classified on other grounds.

While we concur in the division of the remaining lymphomas into lymphocytic and reticulum cell sarcomas, our observations suggest that this division should be effected differently than has been customary in the past. In our 36 cases there were 5 that were clearly lymphocytic sarcoma. Twelve others just as certainly were reticulum cell sarcomas. The difficulty lay in the classification of the remaining neoplasms which fell somewhere between these two extremes. Seven were composed of both anaplastic reticulum cells and the more mature lymphoid elements. In 12 the most anaplastic cells were better differentiated than the reticulum cells and could be described loosely as "lymphoblastic." In previously reported series, the tumors comprising the intermediate group had been categorized in one of two ways, neither of which seemed a priori correct. Sometimes the tumors which were made up of lymphoblasts were grouped with the lymphocytic lymphomas. In other series the classification was determined by the most common cell type even when these were the most mature. When either method was used, the result was a series consisting of about equal numbers of tumors composed of mature (lymphocytic) and immature (reticulum cell) elements. The discouraging feature about this type of classification was that such divisions seemed to have little or no clinical significance. The recurrence

and death rates were about the same for both groups of tumors. Our object was to achieve something more than this and find a method of separation meaningful both to clinicians and pathologists.

RELATION OF HISTOLOGIC SEPARATION OF MATERIAL TO PROGNOSIS

Table II shows the initial separation of our material into the purely lymphocytic and the reticulum cell tumors as well as an intermediate group. It will be seen that when the separation is thus sharply made, the lymphocytic

TABLE II. CORRELATION BETWEEN CELL TYPES AND OTHER PATHOLOGIC FEATURES IN PRIMARY MALIGNANT GASTRIC LYMPHOMA 1935-1955

CELL TYPE	TOTAL	LYMPHATIC METASTASES	INVASION OF ADJACENT ORGANS
Lymphocytic	5	2	0
Reticulum cell	12	12	6
Intermediate	19	16	7
Total	36	30	13

lymphomas, few though they are, differ significantly from the remainder by having fewer instances of lymphatic involvement and offering a better survival rate 3 years after operation (Table III). By contrast, little or no clinical

TABLE III. THREE-YEAR SURVIVAL IN RELATION TO CELL TYPE

CELL TYPE	NUMBER OF CASES ELIGIBLE*	PATIENTS SURVIVING 3 YEARS	
		NUMBER	PER CENT
Lymphocytic	4	4	100
Intermediate	8	2	25
Reticulum cell	6	3	50
Total	18	9	50

*Exclusive of operative deaths and patients not eligible for 3-year follow-up at time of writing.

difference appeared to exist between the moderately and extremely anaplastic tumors. Five of these cases had sufficiently predominant lymphocytic components to suggest that they might have been put into the lymphocytic group if the separation of Thorbjarnarson and associates[2] had been used (Fig. 3, 4, and 5). Two of these patients died of their disease within 3 years, 1 was an operative death, and 2 have not yet been followed 3 years. This gave us no incentive to relax our rigorous method of defining lymphocytic tumors. Similar results kept us from placing special significance on the finding of a major follicular pattern in any of the tumors. None of the lymphocytic tumors showed such a pattern. It was seen in one patient with "lymphoblastoma" and in 4 patients with reticulum cell sarcomas. Of these, 3 are dead of disease, 1 died postoperatively, and 1 has not yet been followed 3 years.

The other possibility was to segregate those cases in which the most anaplastic element was lymphoblastic. If there were a gradation of malignancy from lymphocytic to lymphoblastic to reticulum cell type, the lymphoblastic tumors should exhibit properties midway between the most and least differentiated types. This in fact was not particularly the case. While the lymphoblastic

Fig. 3.

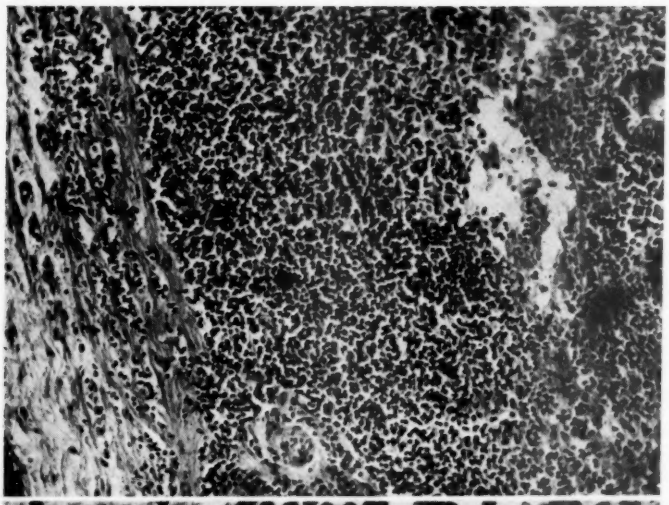

Fig. 4.

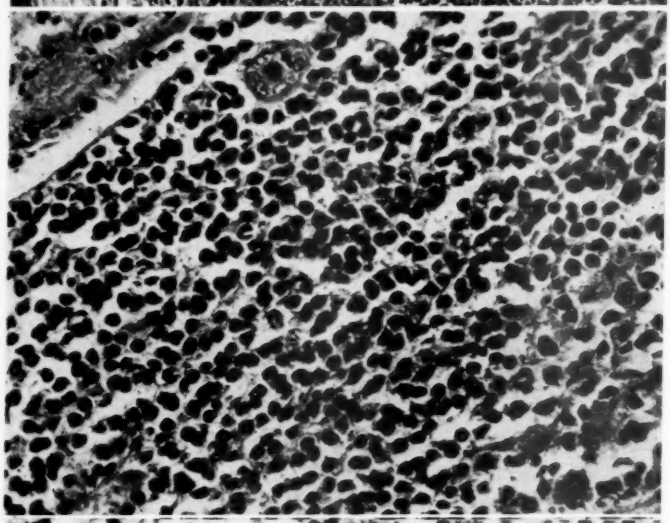

Fig. 5.

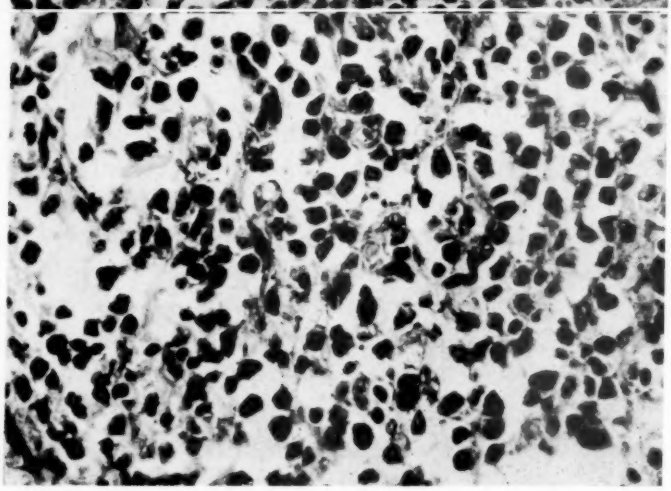

Fig. 3.—Gastric lymphoma in a 45-year-old man who died of disease 33 months after resection. Edge of the main tumor mass. The cells are almost entirely lymphocytes. The tumor is almost completely confined to the lamina propria.

Fig. 4.—Same case as Fig. 3. Separate focus of tumor at the pyloric margin. Here also tumor is lymphocytic and limited to the mucosa.

Fig. 5.—Same case as Figs. 3 and 4. One of the few foci in the main tumor mass in which more anaplastic cells were the dominant type.

sarcomas did show somewhat less tendency to invade other organs and to involve lymph nodes than did reticulum cell sarcomas, the 3-year mortality was higher. Considering those patients who survived operation and were eligible for 3-year follow-up, 3 of 6 or 50 per cent of the patients with reticulum cell sarcomas had survived but only 2 of 7 (29 per cent), with lymphoblastic sarcomas survived.

The only clinically significant separation of our operable gastric lymphomas by cell type lay in the segregation of the 5 purely lymphocytic lymphomas (14 per cent) from the tumors with any less differentiated components. This separation permits us to isolate tumors which clearly are less invasive, less prone to metastasize, and less likely to kill the patient within 3 years of operation at least from all other apparently primary resectable gastric lymphomas (Tables II and III). It is our feeling that the evaluation of a sarcoma containing both lymphocytic and reticulum cell elements is somewhat analogous to the evaluation of a lesion containing both in situ and invasive carcinoma; the presence of the lower grade component does not ameliorate the serious implications of the anaplastic elements. From this point on, the phrase *reticulum cell sarcoma* will be used to include all lymphomas that are not purely lymphocytic.

DISTRIBUTION PATTERNS

Even when the gross tumor mass approximated a sphere, there usually was microscopic evidence of extensive lateral tumor growth. Figs. 3 and 4 illustrate this pattern. In 16 of the 31 cases the connective tissue spaces above and below the muscularis mucosa were infiltrated to an equal extent, but in the other cases there was preference for one plane of extension over the other. On 6 occasions the plane of preference was the submucosa and on 9 it was the mucosal layer. In 7 of these cases the tumor cells were limited to one of these layers providing extremely clear evidence on the question of origin. In 4 cases the tumor cells were limited to the submucosa, but in 3 instances the lamina propria was the only region involved (Fig. 3).

The great tendency for lateral growth seemed to be a result of 2 factors. First of all our material clearly showed that lymphomas extend much more by infiltrating tissue spaces between cells and fibers than by destruction of these elements. The muscular layers, especially the muscularis externa, proved major barriers to tumor expansion. (In the same cases there often was extensive neoplastic infiltration around gastric glands without ulceration.) Obliterating destructive invasion was more commonly seen in the stomach as well as external to it when the tumor was a reticulum cell sarcoma.

Grossly, if it is apparent at all, this lateral extension looks like edema of the stomach wall or rugal hypertrophy. We have seen one submitted case where a lymphosarcoma grew entirely in this fashion. There was no tumor mass as such and the diagnosis was hypertrophic gastritis until microscopic examination.

In itself this lateral extension beyond the bounds of visible and palpable tumor is important because, as Thorbjarnarson and colleagues[2] noted, it suggests that tumor often may be cut across at the resection margin. Our material was not such that we could quantitate this aspect of the margin problem, although we did see a number of instances where incomplete tumor removal had occurred.

We were able, however, to obtain data on a phenomenon of at least equal importance in determining the adequacy of simple resection: the frequency of multiple tumors. Of our 31 operable patients, 5 had grossly visible multiple lymphomatous masses. In addition, in the more or less random selection of sections available for microscopic study, 13 other cases showed other nodules of lymphoma in the stomach wall. Figs. 3, 4, and 5 illustrate this point since each is taken from a different focus of tumor. Altogether then 58 per cent of our resectable cases showed multiple gastric foci while 83 per cent had regional lymph node involvement.

Multiple gastric lesions were seen more often in patients with reticulum cell sarcoma and were usually although not invariably correlated with poor prognosis. This correlation actually was better than the correlation between node involvement and prognosis. The one followed patient with reticulum cell sarcoma who did not have demonstrable node metastases still died of disease within a year. The 5 survivors all had node involvement. This lack of correlation may be compared with the effect of multiple intragastric tumors. Of the patients with reticulum cell sarcoma, 7 of the 9 (78 per cent) with multiple lesions died within 3 years but only 1 of 4 (25 per cent) of the patients with single lesions (despite their node metastases).

Finally, the problem of differentiating between reticulum cell sarcoma and anaplastic gastric carcinoma will be touched on briefly. Not only did many of the reticulum cell sarcomas contain areas of lymphocytic tumor, but in general the nodes and lymphoid follicles of the stomach that were not definitely tumor showed atypical hyperplastic patterns that separated them sharply from carcinomas. Further, no in situ carcinoma was seen.

TREATMENT AND END RESULTS

The 4 inoperable patients were all considered to have disease too advanced for any treatment. All were dead within 3 months. Of the 36 undergoing surgery, 31 (86 per cent) were resectable either by subtotal (17) or total (14) gastrectomy. It is interesting to note the high incidence of total gastrectomy required for the removal of these bulky tumors. As a result, the operative mortality of 22 per cent is not completely unanticipated. It is worthy of note, however, that there have been only 3 deaths in the postoperative period among the last 21 patients treated by resection.

When laparotomy alone was performed, irradiation was given postoperatively in 4 of 5 instances. One of these patients had a massive lesion of the gastric cardia, diagnosed as lymphosarcoma on biopsy. No resection was attempted, but postoperatively tumor appeared in the abdominal wall near the incision. All tumor resolved completely under x-ray therapy and this man is now free of disease 19 years later.

On the basis of our experience, the surgical techniques presently recommended are the standard operative procedures used for treating carcinoma of the stomach. In this series radical subtotal gastrectomy was the method employed most often. Extended total gastrectomy was required for the bulkier lesions, particularly those involving the fundus and cardia.

When postoperative radiation is given we now insist on full therapeutic doses being administered: either the cobalt unit or voltages of one million or more used to deliver a tumor dose of 3,000 to 4,000 r. While the possibility of late complications in the upper abdomen exists with such treatment, such trouble was not encountered in our material.

Postoperative radiation has been administered inconsistently in our series, but there are two considerations that support its routine use. The great incidence of metastases to perigastric lymph nodes and of multiple intragastric tumors furnishes practical support for the belief that all lymphoma present at time of operation may not be eradicated by surgery. From an empirical standpoint we have the fact that 5 of 7 of our 5-year survivors received irradiation. Furthermore we know that, while radiation alone may produce apparent cures in some cases of gastric lymphoma, in others absolutely no beneficial effect is observed. Therefore we believe that irradiation without surgery is not an optimal form of treatment and should be reserved for poor operative risks, inoperable patients, or those for whom an operation if performed at all would obviously be for palliation only. The results reported for radiation alone do not equal the results achieved by combined therapy. It seems logical to take full advantage of the fact that gastric lymphoma may be treated sequentially by two different effective means. We can do nothing but condemn those who use a clinical suspicion of lymphoma as an excuse for avoiding operative investigation of a gastric neoplasm. The operative mortality for gastrectomy in proper hands is now so low that he who would leave in situ an operable tumor of the stomach on the suspicion of sarcoma raised by gross surgical examination or the tentative impressions of frozen section diagnosis is taking into his own hands at one moment not only his "professional reputation but the life of the patient."

F. K., a 27-year-old woman, underwent subtotal gastrectomy for reticulum cell sarcoma in 1941. In 1942 she received heavy radiation therapy for a massive recurrence in the abdominal wall. She remained well for 6½ years, then developed signs of obstruction at the gastroenterostomy stoma in 1948. At operation, the remaining stomach was resected and an entirely new tumor was found, a gelatinous adenocarcinoma. There was no evidence of residual or recurrent sarcoma.

ABSOLUTE FIVE-YEAR SURVIVAL RATE

Among the patients treated by gastrectomy, 6 of 17 (35 per cent) eligible for 5-year follow-up were free of disease at that time. Including the patient cured by radiation alone, the salvage rate is 32 per cent of all patients seen with the primary form of the disease, including 2 with originally disseminated lymphoma. When we include only those cases of unequivocal primary gastric lymphoma, the 5-year survival rate is 7 of 20 (35 per cent). We feel that this last figure is perhaps the fairest evaluation of the present status of the treatment of primary gastric lymphoma.

We must conclude that an adequate gastrectomy followed by x-ray therapy, administered in full therapeutic doses, offers the best opportunity for long-term survival in the treatment of primary lymphoma of the stomach.

CONCLUSIONS

1. Primary, as opposed to secondary malignant lymphoma, is a rare gastric neoplasm comprising 2.2 per cent of all malignant tumors of the stomach seen at Memorial Center from 1931 to 1955.

2. There appear to be no distinguishing features in the clinical diagnosis of primary gastric lymphoma.

3. The 36 cases seen at Memorial Center were classified pathologically as lymphocytic, reticulum cell, and intermediate. Primary gastric Hodgkin's disease was not observed.

4. The demonstration of a high incidence of multiplicity of intragastric lymphomas is the most significant clinicopathologic relationship.

5. Radical surgery plus radiation therapy is the most effective form of treatment.

REFERENCES

1. Craver, L., and Hermann, J.: Abdominal Lymphogranulomatosis, Am. J. Roentgenol. **55**: 165, 1946.
2. Thorbjarnarson, B., Beal, J. M., and Pearce, J. M.: Primary Malignant Lymphoid Tumors of the Stomach, Cancer **9**: 712, 1956.
3. Urban, C., and McNeer, G.: The Relation of the Morphology of Gastric Carcinoma to Long and Short Term Survival, Cancer. In press.

LIPOMA OF THE STOMACH

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THE fortunate patient whose gastric tumor is benign is a rarity. According to large series of clinical and autopsy material, benign tumors of the stomach occur in less than 1 per cent of the cases.[8] Of this small percentage, lipomas have been variously found in 1 to 3 per cent of the total.[8, 9]

The following case report illustrates one of the more serious types of difficulties that may arise in a gastric lipoma, as well as the difficulty in making either a preoperative or operative diagnosis.

CASE REPORT

A. M., a 57-year-old white man, was referred to Jefferson Hospital on April 14, 1957, by Dr. Edward Kotin; the chief complaints were weakness, tarry stools, and epigastric pain. The only significant features in his past medical history were a cerebral vascular accident one year prior to admission from which he had made a good recovery with very few neurologic sequelae, and occasional attacks of epigastric pain. These were usually followed by tarry stools for a few days. In the 2 weeks prior to admission pain became severe and constant. Physical examination on admission was not remarkable other than slight right facial palsy and marked pallor of the skin and mucous membranes. Hemoglobin at this time was 7.4 Gm. Other laboratory studies were within normal limits. Grossly bloody stool was found on rectal examination.

On April 17, barium was given by mouth. No abnormalities were noted in the esophagus or at the esophagogastric junction. A large marginal filling defect was noted in the antral region, occupying the greater curvature. The remainder of the stomach was pliable. Peristalsis passed freely until it reached the antrum. The large mass seemed to ride as a plaque and the opposite wall of the stomach distended about it. The margins were smooth. There was a large central ulcer crater. The duodenal bulb and loop were displaced slightly laterally and anteriorly. The mass did not appear to be fixed to the pancreas. Fluoroscopically the impression was that of malignant ulcer. However, review of the films showed the mass was globular and the ulcer crater was distinct and centrally located. The appearance was very typical of a leiomyoma (Figs. 1 and 2).

No further massive bleeding occurred. Blood replacement was carried out until a normal, stable hemoglobin value was obtained and the patient was operated upon on April 24, 1957. The preoperative diagnosis was gastric tumor with hemorrhage, probably a leiomyosarcoma.

At operation an upper transverse abdominal incision was made and the gastric tumor occupying the antrum was seen. There were no visible or palpable hepatic metastases. The regional nodes were not enlarged with the exception of one node in the gastrichepatic ligament. The tumor was not fixed to the pancreas. A subtotal gastrectomy and omentectomy were performed followed by an antecolic, partial end-to-side gastrojejunostomy. Convalescence was uneventful and the patient was discharged on the eighth postoperative day. The pathologic diagnosis follows.

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Specimen consists of the distal two-thirds of the stomach which was received in the fresh state and which was previously opened. It measures 16.5 cm. along the greater and 12.5 cm. along the lesser curvature. The diameters vary from 10.5 cm. at the proximal resected margin to 6.5 cm. at the distal resected margin. The serosa is pale pink and generally smooth except for some small fibrous strands occurring over a palpable mass present along the anterior surface of the stomach and near the greater curvature at the pyloric end. There is no fixation of the serosa over this mass. When the interior of the stomach is examined, this mass, oval in shape, is found to measure 5.7 by 3.4 by 3.0 cm.

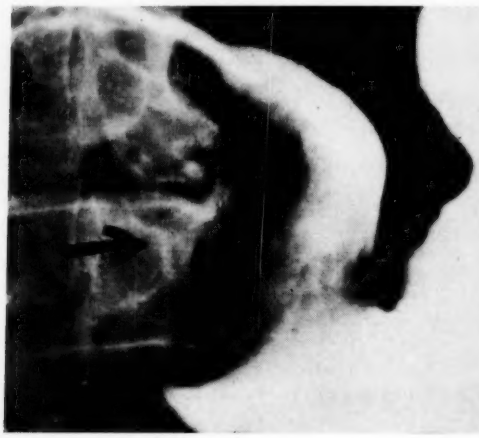

Fig. 1.

Fig. 2.

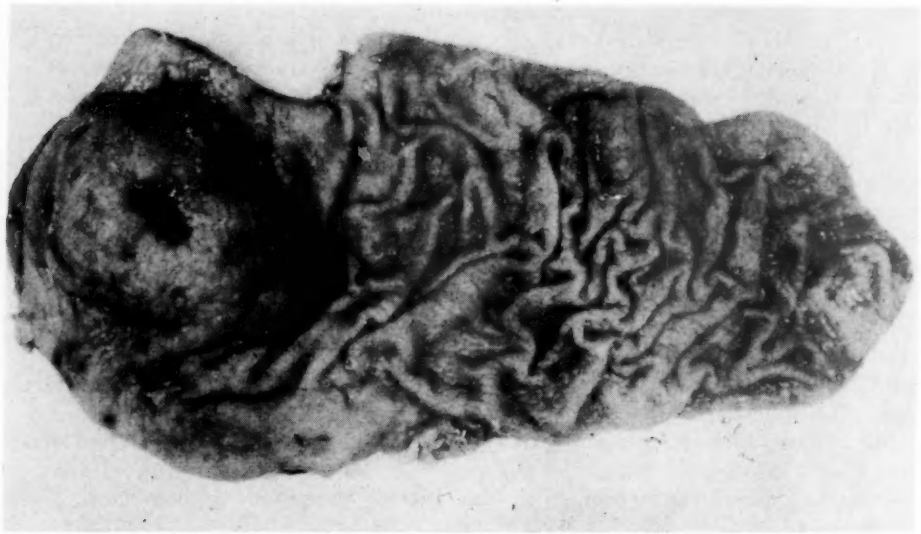

Fig. 3.

The smooth, slightly cobbled, pink-tan mucosa is centrally ulcerated over this mass; the ulceration measures 0.5 cm. in diameter with the mucosa dipping intramurally. Sectioning of this area reveals it to be composed of a well-demarked delicately encapsulated, lobulated, pale yellow, soft, greasy tissue resembling that of a lipoma. No areas of induration are discovered. The ulceration is found to cause an irregularly shaped excavation into this tumor measuring 0.6 cm. in depth and 1.5 cm. in diameter. A thin grey-white area completely circumscribes this ulceration and it is layered by a finely granular grey-white material. Elsewhere the mucosa shows a prominent rugal pattern and the proximal

portion of the specimen is free of induration or ulceration. Attached to the stomach is a pannus of fat in which is found an oval, soft, pale tan lymph node which measures 0.6 cm. in diameter.

Histologic diagnosis is lipoma of the stomach with acute ulceration and chronic lymphadenitis.

DISCUSSION

Most gastric lipomas arise from the submucosa,[6] although cases have been described arising from the subserosa[3] and from the muscularis.[10] Often dumbbell in shape, they may protrude into the lumen of the stomach as well as on the peritoneal surface.[1, 4] Peritoneal thickening over the tumor may be due to inflammatory changes in the lipoma.[7] The most common site of origin is the pyloric region of the stomach, especially the posterior wall. In general, gastric lipomas average about 5 cm. in diameter but very large ones have been reported. When they are situated near the pylorus, intermittent prolapse into the duodenum may cause periodic symptoms of gastric obstruction.[2, 5] Ulceration of the overlying mucosa is common.

The average age at which gastric lipomas have been found is 54 years, approximately the same as for other benign and malignant gastric tumors.[11] There have been no cases reported in patients younger than 29. The incidence is about the same in both sexes.

Gastric lipomas may be entirely asymptomatic and found only during the course of complete gastrointestinal studies.

In those patients presenting themselves with gastric complaints, the symptoms may be caused by mechanical interference of the tumor with gastric emptying, by ulceration of the mucosa over the tumor, by peritoneal irritation, or by hemorrhage. Bleeding occurs rather frequently and may exhibit itself as chronic slow blood loss or may be severe and exsanguinating.

The roentgenologist may be able to differentiate benign from malignant tumors of the stomach, since the usual lipoma is smooth in outline and may be freely movable if in the submucosa, sometimes resembling an intraluminal pedunculated polyp. The radiolucent shadow given by a fatty tumor may be sufficient to permit the preoperative presumptive diagnosis of lipoma. As in the case reported here, the x-ray findings may be extremely similar to those found in gastric leiomyoma or leiomyosarcoma.

Gastroscopy has not proved very helpful in establishing the preoperative diagnosis.

TREATMENT

It is imperative that all gastric lesions be investigated surgically, since the diagnosis of benignity can only be relied upon after accurate histologic examination. In the usual case, even though it may be suspected that one is dealing with a benign gastric tumor, it is our opinion that subtotal gastrectomy should be carried out on the assumption that the lesion may well prove malignant. The procedure should include omentectomy and, depending on the site of the tumor

and the surgical custom of the operator, splenectomy. If the diagnosis of benign gastric lipoma can be made with absolute certainty, local excision is adequate for removal.

SUMMARY AND CONCLUSIONS

A case of benign gastric lipoma has been reported. The symptoms are nonspecific and may resemble those of gastric ulcer or gastric neoplasm. Hemorrhage occurs in a large number of cases; massive bleeding was the presenting symptom in the case reported here. Certain roentgenologic features have been discussed which may enable the roentgenologist to suggest the correct diagnosis. Surgical exploration is indicated in all cases; subtotal gastrectomy is the procedure of choice.

REFERENCES

1. Cattell, R. B.: Lipoma of Stomach Causing Hemorrhage, Lahey Clin. Bull. **3**: 34, 1942.
2. Comfort, M. W.: Submucous Lipomata of the Gastrointestinal Tract; Report of 28 Cases, Surg. Gynec. & Obst. **52**: 101, 1931.
3. Elliott, G. V., and Wilson, H. M.: Mesenchymal Tumors of the Stomach, A. M. A. Arch. Int. Med. **89**: 358, 1952.
4. King, J. M., and Woelfel, G. F.: Submucous Lipoma of the Stomach, Am. J. Surg. **83**: 32, 1952.
5. Klein, N.: A Prolapsed Lipoma in the Duodenal Bulb, Brit. J. Radiol. **23**: 233, 1950.
6. Palmer, E. D.: Benign Intramural Tumors of the Stomach, Medicine **30**: 81, 1951.
7. Phelan, W. J., and Rowan, D. E.: Lipoma of the Stomach, Am. J. Surg. **79**: 469, 1950.
8. Reynolds, M. J.: Submucous Lipoma of the Stomach, SURGERY **10**: 242, 1941.
9. Skorneck, A. B.: Lipoma of the Stomach, A. M. A. Arch. Int. Med. **89**: 615, 1952.
10. Stetten, D.: The Submucous Lipoma of the Gastrointestinal Tract, Surg. Gynec. & Obst. **9**: 156, 1909.
11. Warren, K. W., and Brandenburg, F. H.: Lipoma of the Gastrointestinal Tract, S. Clin. North America **31**: 743, 1951.

INFERIOR MESENTERIC VASCULAR OCCLUSION: SIGMOIDOSCOPIC DIAGNOSIS

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MESENTERIC vascular occlusion remains one of the most lethal of abdominal catastrophes, with no significant reduction in mortality despite many recent advances in surgery. One factor contributing to this high mortality is failure to make an early diagnosis. When mesenteric infarction is confined to the inferior mesenteric vessels, a clinical picture may be produced which can be diagnosed and successfully treated. This clinical picture or syndrome of left colon infarction consists of severe left lower abdominal pain and tenderness, usually accompanied by a bloody rectal discharge.[1] The purpose of this paper is to describe a sigmoidoscopic finding of diagnostic significance in this disease.

SIGMOIDOSCOPIC FINDING

When a bloody rectal discharge is not present in left colon infarction, ischemic mucosal changes may frequently be demonstrated on sigmoidoscopic examination. These ischemic changes represent areas of early hemorrhagic infarction. As the sigmoidoscope is advanced one usually encounters bluish-black areas of ischemic mucosa. These changes may begin in the rectosigmoid or at a higher level, depending upon the condition of the blood supply.

CASE REPORTS

CASE 1.*—E. S., a 68-year-old white man, was admitted to the Los Angeles County Hospital on Jan. 30, 1958, with a 2-day history of sudden left lower abdominal pain, tenesmus, and the passage of bloody bowel movements. He was acutely ill, with a temperature of 101° F. and a pulse of 120. The lower abdomen was markedly tender and rigid, with the signs of diffuse peritonitis. Gross blood was present on rectal examination, and on sigmoidoscopy there were bluish-black areas of mucosal gangrene in the rectosigmoid area. A diagnosis of acute inferior mesenteric vascular occlusion was made, and at surgery there were patchy areas of greenish-black gangrene of the entire left colon including the extraperitoneal rectum. Wide obstructive resection of the left colon was performed, and the distal rectum was oversewn, closed extraperitoneally, and drained. The patient recovered, and 3 months later the transverse colon was anastomosed to the rectum, re-establishing intestinal continuity.

CASE 2.*—H. S., a 72-year-old white man, was admitted to the Los Angeles County Hospital on Nov. 21, 1957, in a state of mental confusion. He had had severe abdominal pain for 3 days. On physical examination he was in a shocklike state, with tachycardia of 120, and was lying in a pool of bloody stool. The abdomen was distended, with generalized

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*Reported in detail elsewhere.[1]

tenderness and rigidity. Dark red blood was found in the rectal ampulla. Sigmoidoscopy showed mucosal necrosis at the 6-inch level, with mottling, cyanosis, and superficial ulceration. A diagnosis was made of occlusion of the inferior mesenteric vessels with infarction of the left colon. At surgery the entire left colon was found to be gangrenous with fresh thrombus occluding the inferior mesenteric artery. A left colectomy with a distal mucous fistula was performed, and the transverse colon was brought out as a colostomy. During the surgical procedure, the patient developed profound shock, with abnormal neurological signs including pupillary inequality and positive Babinski's sign. He expired at the end of surgery. No autopsy was obtained.

CASE 3.—C. B., a 73-year-old white man, was admitted to the Medical Service of the Los Angeles County Hospital on Nov. 6, 1958, with the complaint of sudden severe lower abdominal pain and vomiting. Following the onset of pain he had four diarrheal, blood-tinged stools. On examination there was minimal lower abdominal tenderness. Intermittent lower abdominal pain characterized his course during hospitalization, and 5 days after admission sigmoidoscopy showed cyanotic mucosa with a superficial ulcer at the 6½-inch level, which extended proximally as far as could be visualized. He was considered to have an abdominal aortic aneurysm and mild gastroenteritis. He expired suddenly, and at autopsy the left colon was found to be infarcted and perforated due to thrombotic occlusion of the inferior mesenteric artery. In addition, the abdominal aorta showed arteriosclerotic aneurysmal change.

DISCUSSION

According to Niederstein, the mucous membrane is the most sensitive part of the intestine to ischemic change.[2] Therefore this sign should be present early, making possible the recognition of left colon infarction before such gross manifestations as a bloody rectal discharge.

The sigmoidoscopic demonstration of mucosal ischemic changes may likewise be helpful in the evaluation of undiagnosed bloody diarrhea such as after colorectal anastomoses and abdominal aortic aneurysm resection.

SUMMARY

Sigmoidoscopic examination with the demonstration of ischemic mucosal changes has been described as a simple and available aid in the early diagnosis of acute inferior mesenteric vascular occlusion.

REFERENCES

1. Carter, Richard, Vannix, Robert, Hinshaw, D. B., and Stafford, C. E.: Acute Inferior Mesenteric Vascular Occlusion: A Surgical Syndrome, Am. J. Surg. **98**: 271-275, 1959.
2. Wilson, G. S. M., and Block, J.: Mesenteric Vascular Occlusion, A. M. A. Arch. Surg. **73**: 332, 1956.

IS ILEOSTOMY ALWAYS NECESSARY IN THE SURGICAL TREATMENT OF SEGMENTAL ULCERATIVE COLITIS?

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PATIENTS with segmental ulcerative colitis may successfully undergo colon resection without ileostomy. Such patients may be placed in four main groups depending upon the segment of colon involved: right-sided colitis (regional colitis, enterocolitis, ileocolitis), patchy colitis, left-sided colitis, and diffuse ulcerative colitis but with a normal rectum. A further small group of patients (two in this series) with minimal rectal involvement may have a temporary ileostomy with subsequent reanastomosis when the rectal disease resolves. Segmental colitis has been defined differently in various reports.[1, 5, 9] In this paper the term *segmental colitis* refers to ulcerative colitis in which the colon is not diffusely involved. The senior author believes that right-sided, left-sided, and patchy colitis are different regional manifestations of the same disease. The reported results of operative procedures other than permanent ileostomy in the surgical treatment of segmental ulcerative colitis are reviewed.

Manning and Warren,[7] in a review of their patients with segmental colitis, include all those patients in whom there is no rectal involvement. They report 34 patients in whom primary anastomosis was performed with five deaths. Symptoms were controlled in 55.8 per cent. The disease was arrested in 44.2 per cent. They suggest that ileosigmoidostomy with primary or secondary resection of the diseased colon be attempted in most cases in which the rectum is spared before a decision for ileostomy is reached.

Cooke and Brooke[4] state that ulcerative colitis (diffuse ulcerative colitis), and enterocolitis (right-sided colitis) are different disease entities and should be treated differently. They believe that colon resection should be avoided in the treatment of enterocolitis. They report seven deaths in 16 patients who were operated upon for enterocolitis. Furthermore, Brooke[2] states that resection and anastomosis should have a limited application in the treatment of ordinary ulcerative colitis. Among 131 patients, only 9 were suitable candidates for ileoproctostomy. There were 4 failures. Three patients suffered a recurrence which required permanent ileostomy. There was one death.

Garlock and Lyons[6] divide ulcerative colitis into universal colitis, right-sided colitis, and left-sided colitis. Ileostomy and total colectomy are recommended for universal colitis and left-sided colitis. They advise against proximal colostomy for left-sided colitis, because they believe the colostomy will be difficult to control when the right colon eventually becomes involved. On the other

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hand, in the treatment of right-sided colitis, they favor resection and ileosigmoidostomy before the disease extends to the left colon. Anastomoses were performed in 90 patients of the latter type with an operative mortality of 8.2 per cent. There were 23 failures necessitating permanent ileostomy. They report that most of the failures occurred early in their experience when they failed to appreciate the significance of the persistence of minimal rectal disease.

Cattell[3] advocates ileostomy followed by ileosigmoidostomy and resection of the diseased colon in two stages when the disease is confined to the right colon. In those patients whose disease is limited to the left colon, he advocates a proximal colostomy and resection of the diseased colon, even though the remaining colon will probably become involved at a later date. In his experience, the delay between colostomy and ileostomy will be considerable in some patients. He reports a patient whose colostomy was functioning normally after 19 years. He states that there are "only a few" patients who have segmental disease in which less than a total colectomy is possible. Furthermore, he believes that in only a few patients with ordinary ulcerative colitis in whom ileostomy has been performed will the rectal disease improve sufficiently so that the ileostomy can be taken down and intestinal continuity restored.

Neuman, Bargen, and Judd[8] report 41 patients upon whom they performed resection and anastomosis for segmental colitis. There were six deaths. The disease recurred in 13 of 29 patients followed. Resection and anastomosis was known to be successful, therefore, in 16 of the 41 patients.

REPORT OF CASES

Among 136 patients who have been operated upon for ulcerative colitis between 1939 and 1959, 46 have had segmental disease. This discussion includes all patients whose disease did not involve the entire colon and 2 patients in whom the rectal disease was minimal (total 48 patients). The segment of colon involved in 136 patients is listed in Table I. The limits of colonic involvement were determined by the location of abdominal tenderness, preoperative

TABLE I. LOCATION OF COLITIS IN 136 PATIENTS OPERATED UPON FOR ULCERATIVE COLITIS

Right colon	6
Left colon	19
Patchy (short segment)	7
Diffuse but rectum spared	14
Diffuse with minimal reversible rectal involvement	2
Diffuse	88
Total	136

TABLE II. OPERATIONS PERFORMED FOR SEGMENTAL ULCERATIVE COLITIS

OPERATION	NUMBER OF PATIENTS
Subtotal colectomy and primary anastomosis	22
Subtotal colectomy and proximal colostomy	19
Subtotal colectomy and ileostomy, and secondary takedown of ileostomy and ileocolostomy	
Total	48

barium x-rays, sigmoidoscopy, and the findings at operation. The most reliable signs of colon involvement as seen at operation are injection of the serosa and palpable thickening of the gut wall. See Table II for the operations performed.

SUBTOTAL COLECTOMY AND PRIMARY ANASTOMOSIS

Partial colectomy or bypass and primary anastomosis was performed upon 22 patients between one and 19 years ago. Resection was performed as a second stage in one patient whose colitis was bypassed initially. Nineteen patients have been followed. The location of the colitis and results of resection and anastomosis are listed in Table III. There were 6 patients with right-sided colitis treated by right colectomy and ileotransverse colostomy (4 patients followed), 7 with patchy disease treated by segmental resection (all patients followed), and 9 with extensive disease but a normal rectum and rectosigmoid treated by ileosigmoidostomy (8 patients followed). The colitis has recurred in 5 patients (26 per cent of the patients followed), but, in 3 of these, further resection and reanastomosis was successfully performed with eradication of the disease. Two of the patients with recurrences were treated by permanent ileostomy and are considered failures (10 per cent of the patients followed). Both of these patients are now asymptomatic. One is a 17-year-old girl who developed ulcerative colitis in two colon segments in association with regional ileitis. There were three late deaths due to the following: brain tumor, renal disease, and carcinomatosis (primary carcinoma of the colon present at the initial operation). In each instance there had been no recurrence of the colitis.

TABLE III. RESULTS OF SEGMENTAL RESECTIONS AND PRIMARY ANASTOMOSIS IN THE TREATMENT OF SEGMENTAL ULCERATIVE COLITIS

LOCATION OF DISEASE	LOCATION OF ANASTOMOSIS	TOTAL	NUMBER FOLLOWED	OPERATIVE MORTALITY	LATE MORTALITY*	NO RECURRENCE—PATIENTS ARE ASYMPTOMATIC	RECURRENCE WITH SUCCESSFUL RESECTION	RECURRENCE REQUIRING ILEOSTOMY
Right colon	Ileotransverse colostomy	6	4	0	0	2	2	0
Patchy (short segment)	Colocolostomy	7	7	0	2	4	0	1
Diffuse, but rectum normal	Ileosigmoidostomy	9	8	0	1	5	1	1
Total		22	19	0	3	11	3	2

*Unrelated to surgical treatment.

Five of the 14 patients who are considered to have good results state that they experience loose stools for a day or two several times a year. In some, these episodes appear during periods of nervous stress.

COLOSTOMY

In 19 patients whose disease was confined to the left colon, a colostomy was performed proximal to the diseased bowel. The diseased colon was resected primarily in most instances. Among 18 patients followed, the retained colon has remained free of disease in 6 (Table IV). The colostomy proved to be temporary in 12 patients due to a recurrence of disease in the remaining colon. Further colon resection and ileostomy were performed in this group within an average of 4 years. It is of interest that 5 patients suffered a recurrence or extension of disease requiring ileostomy within one year. Six patients remained free of colitis for 2 to 16 years before ileostomy became necessary. Six patients have had a normally functioning colostomy for an average of 10 years. The longest period is 22 years. There was no operative mortality in this series. Two late deaths have occurred. One was caused by an unsuspected carcinoma which developed in the retained cecum in a patient who was temporarily lost to follow-up.

TABLE IV. FUTURE OF COLOSTOMY IN 18 PATIENTS WITH LEFT-SIDED ULCERATIVE COLITIS

DURATION OF COLOSTOMY IN YEARS	TOTAL PATIENTS WITH COLOSTOMY	PATIENTS IN WHOM COLOSTOMY WAS REPLACED BY ILEOSTOMY BECAUSE OF RECURRENCE	PATIENTS WITH NORMALLY FUNCTIONING COLOSTOMY WITHOUT RECURRENCE
0- 2	18	7	1
2- 5	10	0	2
5-10	8	3	1
10-15	4	0	0
15-20	4	1	2*
Over 20	1	0	1
Total		11	7

*Patient died of carcinoma of colon but without recurrence of colitis.

SECONDARY ANASTOMOSIS AFTER TEMPORARY ILEOSTOMY

Delayed anastomosis with takedown of the ileostomy was performed in 7 patients. In 5 patients, the rectum was free of disease. In 2 patients with minimal rectal disease, reanastomosis was carried out when all evidence of rectal disease had disappeared.

Ileosigmoidostomy failed in 2 patients because of the appearance of rectal inflammation. One patient had had rectal involvement initially and one had not. One of these was anastomosed a second time and is comfortable despite occasional mild flare-ups in the rectal segment. Two other patients have similar periodic exacerbations of rectal inflammation during emotional crises, but generally are well. One patient developed a ring of granulation tissue involving the lower 3 or 4 cm. of the rectum. This has healed leaving a stenotic area which can be satisfactorily dilated by the patient. Three patients are asymptomatic.

DISCUSSION

This report represents a review of 46 patients, all of whom underwent definitive surgery for segmental ulcerative colitis and two patients with diffuse colitis but with minimal reversible rectal disease. During the same period, 88 patients with diffuse ulcerative colitis were treated by permanent ileostomy.

The majority of patients requiring operative treatment for ulcerative colitis have diffuse disease which is best treated by ileostomy and total colectomy. In such patients, a permanent ileostomy is an acceptable price for rehabilitation and good health. However, in those patients in whom the disease does not involve the entire colon, ileostomy can be avoided in many instances by resecting the diseased colon and performing a primary anastomosis if the distal colon is normal, or colostomy if the proximal colon is uninvolved.

A review of our series reveals that by confining the resection to the diseased colon, there is a reasonable chance that the disease will be permanently arrested.

The disease was successfully eradicated in 17 of 19 patients treated by segmental resection. Excluding the three late deaths, there are 14 patients of this group who are free of colitis. Only 2 of the 19 patients now have an ileostomy.

In patients with segmental disease involving the left colon, colostomy may be established proximal to the disease. The colostomy may be permanent, particularly if the colitis does not recur within the first year. If, on the other hand, ileostomy becomes necessary due to subsequent extension of disease to the remaining colon, the period of delay may be significantly long. We believe that the possibility of avoiding or, at least, delaying ileostomy and the inconvenience of an ileostomy bag outweighs the added risk and discomfort of another operation. The development of carcinoma in the retained proximal colon following colostomy represents a risk of this treatment. In our opinion, however, the danger of malignant degeneration does not contraindicate the use of colostomy in patients who can be followed carefully.

A small group of patients in this series had diffuse colitis associated with reversible rectal and rectosigmoid disease. This is an unusual occurrence in our experience. We rarely see moderate or severe rectal involvement improve sufficiently to permit reanastomosis.

SUMMARY AND CONCLUSIONS

Ileostomy and total colectomy are not always necessary in the surgical treatment of ulcerative colitis.

In patients with segmental disease located proximal to the rectosigmoid, resection of the involved colon and primary anastomosis will be successful in most instances. Of 22 patients so treated in this series, there were no operative deaths and three unrelated late deaths. Fourteen of the 19 patients followed are presently well and are without symptoms or signs of colitis. Two patients have had a recurrence of colitis and have had an ileostomy performed.

In patients whose colitis is limited to the left colon, subtotal colectomy and proximal colostomy may halt the progression of the disease. Six patients have had a normally functioning colostomy for an average of 10 years. The longest period is 22 years. If the colitis extends to the proximal colon segment, subtotal colectomy and ileostomy may be done with very little added risk. There was no operative mortality in this series. During the period before the colitis

recurs, the patient is more comfortable with a colostomy than with an ileostomy which requires a bag. The delay averaged 4 years in the 11 patients in whom an ileostomy replaced a colostomy.

A small group of patients with diffuse ulcerative colitis may have a normal or minimally diseased rectum. There were 7 such patients in this series. All were treated by ileostomy and secondary ileosigmoidostomy or ileoproctostomy. In 5 patients, this treatment has been successful while 2 patients have suffered an exacerbation of their rectal disease requiring ileostomy. One of the 2 patients subsequently has had a reanastomosis.

REFERENCES

1. Bockus, H. L.: Gastroenterology, Vol. 2, Philadelphia, 1944, W. B. Saunders Co.
2. Brooke, B. N.: The Outcome of Surgery for Ulcerative Colitis, Lancet **2**: 532, 1956.
3. Cattell, R. B.: Discussion on the Surgery of Ulcerative Colitis, Proc. Roy. Soc. Med. **46**: 1021, 1953.
4. Cooke, W. T., and Brooke, B. N.: Non-specific Enterocolitis, Quart. J. Med. **24**: 1, 1955.
5. Crohn, B. B., Garlock, J. H., and Yarnis, H.: Incidence of Right-Sided Colitis (Segmental), J. A. M. A. **134**: 334, 1947.
6. Garlock, J. H., and Lyons, A. S.: The Role of Surgery in the Therapy of Ulcerative Colitis, Gastroenterology **26**: 709, 1954.
7. Manning, J. H., Warren, R., and Adi, A. S.: Segmental Colitis, New England J. Med. **252**: 850, 1955.
8. Neuman, H. W., Bargen, J. A., and Judd, E. S.: A Clinical Study of 201 Cases of Regional (Segmental) Colitis, Surg. Gynec. & Obst. **99**: 563, 1954.
9. Warren, S., and Sommers, S. C.: Pathology of Regional Ileitis and Ulcerative Colitis, J. A. M. A. **154**: 189, 1954.

INHERITANCE OF GALL-BLADDER DISEASE

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THE purpose of this paper is to present data on the families of 100 consecutive patients having gall-bladder surgery at our institution. This systematic study was undertaken after the casual observation of the presence of gallstones in several members of many families. This study suggests that chronic cholecystitis, cholelithiasis, and cholesterosis are part of one dominantly inherited disease.

METHODS

The relatives of 100 consecutive patients having gall-bladder or biliary duct surgery in our institution in 1956 and 1957 were investigated for the presence or absence of gall-bladder disease. The patients were questioned about their relatives, the relatives were studied by cholecystography, when possible, and the reports of surgery or autopsy examinations were obtained. Definite evidence of gall-bladder disease was considered to be established by gall-bladder x-rays showing stones, polyps, or a nonfunctioning gall bladder; the operative report of gall-bladder disease; or in a few instances the report that the patient had actually seen the stones of a parent. In addition, 3 cases were placed in this category solely because of a good history of colic and jaundice in a parent.

RESULTS

The summarization of the data on this study (Table I) indicates that definite evidence of gall-bladder disease was found in the mother or father of 33 of the 100 patients. In 2 cases evidence was obtained that neither parent had gall-bladder disease: in one case the gall-bladder x-rays of both parents were

TABLE I. SUMMARIZATION OF DATA FROM THE FAMILY STUDIES OF 100 CONSECUTIVE GALL-BLADDER OPERATIONS

	NUMBER	PER CENT	AVERAGE AGE	FATHER OR MOTHER WITH DEFINITE GALL-BLADDER DISEASE	NEITHER PARENT WITH GALL-BLADDER DISEASE	DEFINITE OR SUGGESTIVE EVIDENCE OF GALL-BLADDER DISEASE IN SIB, PARENT, OR CHILD
Men	27	27	55	7	0	16
Women	73	73	48	26	2	56
Total	100			33	2	72 (%)

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negative even though one parent had indigestion suggestive of gall-bladder disease; in the other case the gall bladder of the mother was found to be grossly normal when palpated at surgery for colon malignancy and the father's gall-bladder x-ray was normal. Definite information to establish or exclude gall-bladder disease in *both* parents of each of the other 65 patients was not obtainable although it may yet be possible to obtain information about the parents of some patients. Definite or suggestive evidence of gall-bladder disease was obtained in a sibling, parent, or offspring of 72 per cent of the patients. Fig. 1 illustrates selected pedigrees from this series.

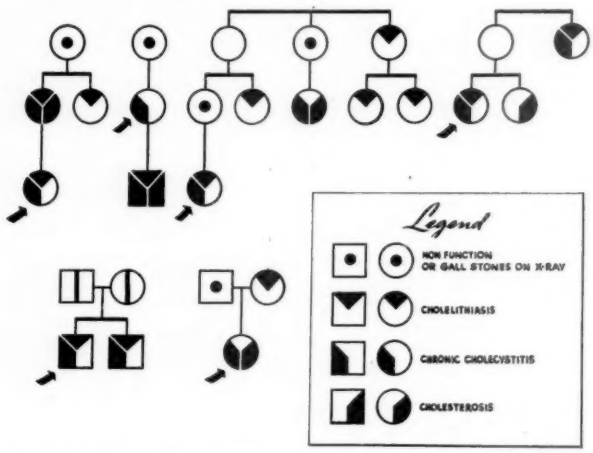

Fig. 1.—Selected pedigrees from series. Arrow indicates the propositus patient. The squares indicate males and the circles indicate females. The vertical lines through the figures at the lower left-hand pedigree indicate that the individuals probably had gall-bladder disease though definite information was not obtainable.

DISCUSSION

Although gall-bladder disease is quite common (affecting 10 to 20 per cent of the adult population[3]) very little work has been done regarding the hereditary etiologic factors. In 1920 Barker[2] stated that many clinicians had gained the impression that gall-bladder disease is much more common in some families than in others despite lack of actual proof of the part heredity plays in the etiology of gall-bladder disease. In 1925 Huddy[7] reported that 42 per cent of 57 patients with gall-bladder disease gave a history of indigestion in other relatives whereas only 16 per cent of control patients gave a history of indigestion in any relatives. Huddy also presented a pedigree of gallstones present in three generations of one family. Mareuse[13] (1929) described a family in which 17 cases of cholecystitis were found in one family. He postulated an irregular dominant mode of inheritance. Körner[11] in 1937 collected 74 pedigrees of families with gall-bladder disease and showed that gall-bladder disease was 5 times as common in the families of affected individuals as in the families of the control group. Dixon and Owen[4] in 1952 reported three families in which gallstones were prevalent. Littler and Ellis[12] in 1952 reported that "20.8 per cent" of their 100 patients with gallstones gave a positive family history of this disease. Hagy[6] in 1955 reported 7 cases of cholecystitis in three generations of one family. Rinaldo and Baltz[15] in 1957 reported a family in which 8 of 11 members of two generations had gallstones or suggestion of gallstones.

Tesler[16] in 1946 reported identical twin girls with gall-bladder disease. Kennard[10] reported identical twin girls and their mother with chronic cholecystitis, cholelithiasis, and cholesterosis. Ivy,[8] in reporting ulcers in identical twin males, reported also the presence of gall-bladder disease in one. Further inquiry into this family revealed that the other twin and their mother probably had gall-bladder disease. Doig and Pitman[5] reported concordance of cholelithiasis in two male identical twins but not in two female identical twins. Further more extensive twin studies should prove helpful in elucidating the importance of heredity in gall-bladder disease.

The term *gall-bladder disease* used here would seem at first to be a rather vague term covering perhaps a heterogeneous group of conditions. We feel, however, that these genetic studies tend to make a homogeneous disease from several apparently distinct conditions. A list of pathologic diagnoses (Table II) found in our series demonstrates the overlapping of the conditions of chronic cholecystitis (94 per cent) with that of cholelithiasis (92 per cent) and cholesterosis (28 per cent). The coexistence of these conditions tends to suggest that they are part of one disease with variable manifestations. In the selected pedigrees shown in Fig. 1 it may be noted that chronic cholecystitis, cholelithiasis, and cholesterosis alone or in various combinations may appear in different members of the same family. This also suggests that these are all manifestations of one disease. If gall-bladder disease could be characterized more specifically biochemically, genetic studies could be more exact than is possible now on a pathologic basis. Recent electrophoretic studies of bile[9, 17] suggest that this type of study may be helpful in classifying gall-bladder disease metabolically.

TABLE II. SUMMARIZATION OF PATHOLOGIC DIAGNOSES OF THIS SERIES OF 100 CASES

DIAGNOSES	NUMBER OF CASES
Cholelithiasis	5
Chronic cholecystitis	3
Chronic cholecystitis with polyps or papillomas	2
Chronic cholecystitis with cholelithiasis	61
Chronic cholecystitis, papillomas, and cholelithiasis	1
Chronic cholecystitis, cholelithiasis, cholesterosis	23
Chronic cholecystitis, cholelithiasis, papillomas, cholesterosis	1
Chronic cholecystitis, papillomas, cholesterosis	3
Cholelithiasis and cholesterosis	1

Our studies suggest that gall-bladder disease is inherited as a dominant condition—that is, if an individual has the disease, one or other of the parents must also be affected. One possible objection to a theory of the dominant inheritance of gall-bladder disease would be the two apparent exceptions mentioned in this series. An intriguing theory which would explain an incidence of gall-bladder disease among females approximately twice that of males is the inheritance of the disease as a sex-linked dominant disease (as carried by a gene on the nonhomologous portion of the X chromosome). Fig. 2 demonstrates this mode of inheritance. It will be noted that a man would inherit a sex-linked dominant disease[16] only from his mother and would pass it on to all of his

daughters but to none of his sons. A woman, however, would pass the disease on to one-half of the daughters and one-half of the sons. We have found this concept very useful clinically and have found but two possible exceptions within this study—the mothers of two of the men were found to have normal gall-bladder x-rays although each had unexplained digestive symptoms. If the sex-linked dominant mode of inheritance is correct, one must explain these apparent exceptions by either a decreased penetrance of the gene or by the inadequacy of our present x-ray techniques. It is well known that the present cholecystographic techniques are not perfect. Baker and Hodgson[1] reported pathologic gall-bladder disease (at surgery) in 5.6 per cent of 568 patients whose gall bladders were reported as normal by oral cholecystography. It is planned to study the parents of a large number of male patients with gall-bladder disease in order to test more adequately this hypothesis. We have been unable in the meager literature on the inheritance of gall-bladder disease to find evidence which would preclude this sex-linked dominant mode of inheritance.

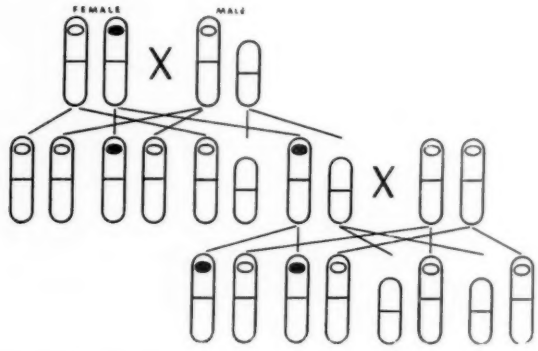

Fig. 2.—Illustration of the dominant sex-linked mode of inheritance.

Pregnancy is well known as an aggravating factor in gall-bladder disease and may be considered a factor in explaining the earlier age of onset in the female. Certainly environmental factors are important in modifying the disease in hereditarily susceptible individuals. The stressing of the importance of heredity in the etiology of gall-bladder disease does not exclude the possibility that there may be important environmental factors in some cases. The recognition that gall-bladder disease occurs, at least in some instances, as a genetic condition is not only helpful clinically but may also eventually provide some insight into the basic biochemical defect causing the disease.

SUMMARY

The families of 100 consecutive patients undergoing gall-bladder operations were studied for the presence of other cases of gall-bladder disease. In 72 per cent of these families definite or suggestive evidence of gall-bladder disease was found in a parent, sibling, or child of the patients. One or the other of the parents of 33 patients was found to have *definite* evidence of gall-bladder disease. It was not possible to obtain definite information to establish or exclude gall-bladder disease in both parents of 65 of the patients. The coexistence of

chronic cholecystitis, cholelithiasis, and cholesterosis in the series of patients and in different members of the same families suggests that these conditions are all a part of one inherited disease. The evidence in this series suggests that gall-bladder disease may be inherited as a dominant condition with a possibility that it may be inherited by a sex-linked dominant mode.

REFERENCES

1. Baker, H. L., and Hodgson, J. R.: Oral Cholecystography: An Evaluation of Its Accuracy, Gastroenterology **34**: 1137, 1958.
2. Barker, L. F.: Hints for Diagnosis of Disease of Gall Bladder and of Biliary Passages, J. A. M. A. **75**: 1105-1109, 1920.
3. Cunningham, J. A., and Hardenbergh, F. E.: Comparative Incidence of Cholelithiasis in the Negro and White Races, A. M. A. Arch. Int. Med. **97**: 68, 1956.
4. Dixon, C. F., and Owen, H. W.: Cholelithiasis: Familial Predisposition, S. Clin. North America **32**: 1177, 1952.
5. Doig, R. K., and Pitman, F.: Illness in Twins: 1. A Study of Twins From a General Hospital Population, M. J. Australia **44**: 612, 1957.
6. Hagy, G. W.: Concentration of Gastric Carcinoma, Peptic Ulcer, and Cholecystitis in a Family Group, Am. J. Human Genet. **7**: 386-397, 1955.
7. Huddy, G. P. B.: A Study of the Family Histories of 300 Patients Suffering From Chronic Upper Abdominal Lesions, Lancet **209**: 276-278. 1925.
8. Ivy, A. C., and Flood, F. T.: Is Susceptibility to Peptic Ulcer Inherited? Occurrence of Ulcer in Identical Twins, Gastroenterology **14**: 375-381, 1950.
9. Juniper, Kerrison, Jr.: The Relationship of a Biliary Lipoprotein Complex to Some Theories of Gallstone Formation, Am. Surgeon **24**: 45-56, 1958.
10. Kennard, J. H.: Cholelithiasis in Identical Twins, New England J. Med. **252**: 1131-1132. 1955.
11. Körner, G.: Über die familiäre Häufung der Gallenblasenkrankheiten, Ztschr. menschl. Vererb.-u. Konstitutionslehre **20**: 526-582, 1937.
12. Littler, T. R., and Ellis, G. R.: Gall-stones: A Clinical Survey, Brit. M. J. **1**: 842-844, 1952.
13. Marcuse, M.: Zur Erblichkeit der Psoriasis und der Cholezystitis (Cholelithiasis) und über die Verbreitung beider Leiden in einer Familie, Arch. Rass. u. Ges. Biol. **22**: 50-51, 1929.
14. Neel, J. V., and Schull, W. J.: Human Heredity, Chicago, 1954, University of Chicago Press, p. 44.
15. Rinaldo, J. A., and Baltz, J. I.: Familial Cholelithiasis, With Special Reference to Its Relation to Familial Pancreatitis, Am. J. Med. **23**: 880-885, 1957.
16. Tesler, J.: Cholecystitis, and Cholelithiasis in Identical Twins, Gastroenterology **7**: 685, 1946.
17. Verschure, J. C., DeWael, J., and Mijnlieff, P. F.: Further Investigations on the Macromolecular Complex in Human Biles, Clin. chim. acta, Amsterdam **1**: 511-518, 1956.

INTESTINAL OBSTRUCTION CAUSED BY IMPACTED GALLSTONES

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IT IS generally agreed that intestinal obstruction due to gallstones is of infrequent occurrence and that the high mortality rate encountered with this condition is due in the majority of instances to late recognition and delay in surgical treatment. Age and its accompanying disorders, principally arteriosclerosis, contribute to a fatal outcome in many of these patients. Because gallstone ileus is an uncommon type of intestinal obstruction, we felt it of interest to report our experience in treatment of 10 patients with this condition seen during the period 1947 through 1958. Data concerning these patients are summarized in Table I and are discussed below.

TABLE I. CLINICAL COURSE IN 10 PATIENTS WITH INTESTINAL OBSTRUCTION DUE TO GALLSTONES

NAME	SEX	AGE	DURATION OF CHOLELITHIASIS (YEARS)	ROENTGEN EXAMINATION	PREOPERATIVE DIAGNOSIS	LOCATION OF OBSTRUCTION	EXPLORATION OF RIGHT SUBHEPATIC REGION	POSTOPERATIVE COMPLICATIONS	RESULTS
1. K. E.	F	83		Technically unsatisfactory	Ileus	Distal ileum		Wound infection	Cured
2. K. M.	F	61	4	Fluid levels	Appendicitis	Distal ileum	Adhesions	None	Cured
3. M. S.	F	63			Incarcerated hernia	Jejunum	Adhesions	Wound infection	Cured
4. F. P.	M	57	6	Fluid levels	Gallstone ileus	Distal ileum	Adhesions, cholelithiasis	Wound infection	Cured
5. J. S.	M	63	8	Normal	Subacute appendicitis	Distal ileum			Died during operation*
6. M. H.	F	71	30	Fluid levels	Gallstone ileus	Distal ileum		Cystitis	Cured
7. A. V.	F	66	2	Normal	Gallstone ileus	Distal ileum	Adhesions	Parotitis	Cured
8. B. K.	F	52	20	Fluid levels	Gallstone ileus	Distal ileum	Adhesions, cholelithiasis	Wound infection	Cured
9. M. M.	F	57	5	Fluid levels	Gallstone ileus	Distal ileum	Adhesions, cholelithiasis	Slight icterus	Cured
10. A. C.	F	73	35	Barium meal; contrast impeded in distal ileum	Gallstone ileus	Distal ileum		Wound infection	Cured

*J. S.: Autopsy findings included cholelithiasis, two fistulas, chronic intestinal obstruction with perforation of the ileum and suppurative peritonitis.

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INCIDENCE, SEX, AND AGE

Foss and Summers[6] report gallstones as a cause of obstruction in 0.68 to 5.3 per cent of all cases of intestinal obstruction. Of 484 patients operated upon for intestinal obstruction, Deckoff[4] found 12 with obstruction due to gallstones, an incidence of 2.5 per cent. In our experience, gallstones were the cause of obstruction in 1.7 per cent of patients operated upon for mechanical obstruction (10 of a total of 583 patients). Eighty per cent of our patients with gallstone ileus were seen during the second 6 years as compared to only 20 per cent seen during the first 6 years of the period covered. Patients ranged in age from 52 to 83 years. The sex ratio was 4 females to 1 male. Similar values for age and sex are reported.

PATHOLOGY

The calculus may enter the gastrointestinal tract by one of two routes. (1) Smaller stones may pass via the choledochus and papilla of Vater into the duodenum. In this instance, at the time of operation, the gall bladder will be found free of adhesions.[19] (2) The usual site of entry of the gallstone is via a pathologic communication between gall bladder and an adjoining hollow viscus. Bernhard[2] reports that biliary-enteric fistulas occur in the duodenum, stomach, and colon in a ratio of 6:3:1. The passage of a calculus into the intestinal tract does not necessarily imply obstruction will occur; of Bernhard's 109 patients with internal biliary fistulas, none developed gallstone obstruction. In all of 6 patients in our series in which the subhepatic area was explored at the time of operation, adhesions suggestive of the presence of a cholecystoduodenal fistula were found. In one patient, two fistulas were found at autopsy.

PAST HISTORY

Reported experiences are not in agreement regarding a history of cholelithiasis. Some surgeons have found gallstone ileus to be the first manifestation of cholelithiasis. Others report previous biliary tract disease in 58.3 to 77 per cent of patients.[4, 11, 12] In the present series, 8 patients had experienced biliary colic from 2 to 35 years prior to the development of intestinal obstruction.

SYMPTOMATOLOGY

The symptoms of gallstone ileus depend upon the presence or absence of clinical signs of the cholecystoenteric fistula, the size of the calculus, the site of obstruction, and the degree of reflex spasm of the bowel wall. It seems likely that some fistulas present with severe biliary colic, others with mild symptoms, and the remainder with no apparent change in the patient's health. The subjective complaints of many patients are strikingly similar: pain of sudden origin in the right hypochondrium or in the epigastrium which soon assumes a colicky character and spreads over the entire abdomen eventually concentrating in the right or left hypogastrium (Patients 1, 2, 3, 4, 8, 9, and 10 of Table I). The migratory character of the pain may simulate appendicitis, especially if it is constant and not colicky. From our experience we consider the latter type of

pain characteristic of gallstone ileus. Vomiting and intermittent failure to pass gas or stools are almost always present; obesity and dehydration have been common findings also.

Tympany and tenderness of the abdomen were present in 10 patients. Tenderness was located in the right hypogastrium in 5 patients, in the left hypogastrium in 2, in both lower quadrants in one patient, and was diffuse in 2 patients. Tenderness to palpation over the gall-bladder area could be elicited in only one patient; evidently the symptoms referable to the obstruction overshadow the signs of the cholecystoduodenal fistula.

Polymorphonuclear leukocytosis (average 14,700) was found in 6 patients out of 7. Hemoconcentration secondary to the obstruction is apparently not responsible as the red cell count was normal. Inflammation around the enterobiliary fistula was, at least in part, the cause of the leukocytosis.

ROENTGEN EXAMINATION

In favorable cases, radiographic studies may establish the correct diagnosis. Unfortunately, such cases appear to be exceptional.[4] The flat film may reveal an opacity in the intestinal loops (if the stone is opaque). At times a gallstone which had been visualized at a previous examination will be found to be no longer visible in the gall-bladder area. Air in the biliary passages may indicate the presence of an internal biliary fistula. Accurate diagnosis may be obtained by oral barium as recommended by Bauer[1] and others; however, we believe the overdistention of the bowel with barium and other disadvantages inherent in its use outweigh the advantage of making a precise etiologic diagnosis in patients with clinical signs of intestinal obstruction. Flat films of the abdomen were performed in 8 patients; in no case did it help to clarify the situation. Fluid levels were apparent in the x-ray of 5 patients; physiologic distention of the bowel with gas was shown in two instances and the film of one patient was not satisfactory for evaluation because of obesity. X-rays after oral administration of barium had been performed in one patient; it demonstrated the type and location of the obstruction.

DIAGNOSIS

The diagnosis of intestinal obstruction in patients with gallstone ileus is usually not difficult. However, a survey of the literature reveals that the percentage of accurate diagnoses as regards the cause of the obstruction is not high. Coffey and Willox[3] report 30 per cent and Deckoff[4] 50 per cent accurate etiologic diagnoses. The correct preoperative diagnosis was made in 6 patients (60 per cent) of the present series. In two patients, the condition was mistaken for appendicitis. In retrospect, the diagnosis in J. S. (Case 5) was almost impossible because: (1) the patient was a man; (2) he was not obese; (3) on admission to the surgical ward, the symptoms of intestinal obstruction ceased; (4) no dehydration was present; (5) flat film of the abdomen demonstrated no abnormality; (6) there was constant local tenderness in the right hypogastrium; and (7) leukocytosis was present. Under these circumstances, the most likely diagnosis seemed to be appendicitis.

TREATMENT

The only appropriate therapy of gallstone ileus is early operation. The blocking stone is best removed by longitudinal incision of the bowel. Whether the incision is closed longitudinally or transversely is of little importance. We have never tried the maneuver of squeezing the calculus through the site of impaction aborally with the intention of its spontaneous elimination. The recommendation of Wangensteen[20] to remove the gallstone aseptically by insertion of Halsted mattress sutures prior to incision has not been tried but seems worthwhile. In all our patients, the gallstone was removed by longitudinal incision and transverse suture of the intestinal wall. Gangrenous bowel required resection in one instance. All patients received routine treatment for obstruction as well including correction of fluid and electrolyte deficits and aspiration of intestinal content via a Miller-Abbott tube.

Fig. 1.—X-ray examination after oral barium (Patient A. C., Case 10, Table I). The contrast material is seen to be impeded in the distal ileum (left lower corner of film).

As to the location of the intestinal obstruction, the calculus was impacted in the distal ileum in 9 patients and in the jejunum in one patient. Other sites of obstruction have been reported: pylorus,[9] the first part of the duodenum,[13] and colon.[3, 5, 17] The impacted gallstones in our material varied in size from that of a plum to that of an apple. Apparently the largest calculus removed from the bowel is that reported by Grey-Turner,[7] which measured 17.7 cm. in diameter.

Simultaneous intervention for both obstruction and repair of the fistula was first recommended by Holz.[8] The question of treatment of the cholecystoduodenal fistula at the time of operation for obstruction poses no problem. We do not repair the fistula in this situation since the laborious isolation of the

involved structures with reconstruction of both biliary passages and duodenum prolongs the operation beyond the tolerance of the patient. We agree with Mossimann[11] that further surgery should be undertaken in those patients in whom persistent fistula (mostly cholecystocolic) gives rise to recurrent cholangitis.

POSTOPERATIVE COMPLICATIONS

Recurrent bowel obstruction due to gallstones has been reported but is infrequent. Until 1952, only 10 cases were recorded in the Anglo-American literature.[14] The recurrence occurred either shortly after the first operation (7 to 11 days)[16, 18] or after a longer period (2 to 13 months).[14, 15] No recurrent episodes of gallstone obstruction were observed in the present series. The most frequent postoperative complication was pyogenic wound infection which occurred in 5 patients. Other complications were of minor significance.

MORTALITY AND RESULTS

Postoperative mortality rates in patients with gallstone ileus as reported by earlier authors have been high and rates up to 50 per cent[6] have been recorded. The universally accepted principles for treatment of intestinal obstruction as introduced by Wangensteen have influenced the results of the operative treatment of this condition so that in the last 10 to 15 years mortality rates have been reduced to 12.5 per cent[12] and 8.3 per cent.[4] In the present series, one patient died. This mortality rate of 10 per cent compares favorably with other series.

We believe the prognosis and results of treatment of patients with gallstone ileus may be further improved if the general diagnosis of intestinal obstruction is made early and the basic principles of treatment of intestinal obstruction are strictly followed.

SUMMARY

1. Ten patients operated on for gallstone ileus during the years 1947 through 1958 are presented.

2. The disease occurred four times more frequently in women than in men; the average age was 64.6 years.

3. A past history of previous biliary disease was obtained in 80 per cent of cases.

4. The typical subjective complaint was found to be pains of migratory character which began under the right costal margin and were severe and constant; after a shorter or longer time interval colic occurred, spreading all over the abdomen and finally localizing in the lower quadrants, especially in the right one. This type of pain was present in 70 per cent of cases.

5. Flat films of the abdomen usually do not reveal the cause of ileus. In 5 of 8 patients studied, x-ray showed fluid levels; in 3 it was unrevealing. One patient was examined after oral barium and the location of the obstruction was demonstrated.

6. The correct preoperative diagnosis was made in 60 per cent of patients.

7. The obstruction occurred in the distal ileum in 9 patients and in the jejunum in one.

8. Manual exploration of the subhepatic areas was performed during operation in 6 patients and in each adhesions were found to suggest the presence of a cholecystoduodenal fistula.

9. Simultaneous surgical treatment of both ileus and the fistula is believed to be associated with undue risk. Surgery for the fistula in a later period is indicated only in patients with recurrent cholangitis.

10. The mortality rate was 10 per cent.

11. Improvement of therapeutic results may be expected from improved diagnosis of intestinal obstruction in general and from strict adherence to the basic principles of modern treatment of obstruction.

Revision of this paper was by Dr. John F. Perry, Jr., Department of Surgery, University, of Minnesota Hospitals, Minneapolis.

REFERENCES

1. Bauer, P. A.: Trois cas d'iléus biliaire, Radiol. Clin. (Basel) **24**: 302, 1955.
2. Bernhard, F.: Die spontanen Gallenfisteln und ihre operative Behandlung, Deutsche Ztschr. Chir. **242**: 493, 1934.
3. Coffey, R. J., and Willox, G. D.: Gallstone Obstruction of Intestinal Tract, Am. J. Surg. **18**: 286, 1952.
4. Deckoff, S. L.: Gallstone Ileus, Ann. Surg. **142**: 52, 1955.
5. Diviš, J.: Personal communication.
6. Foss, H. L., and Summers, J. D.: Intestinal Obstruction From Gallstones, Ann. Surg. **115**: 721, 1942.
7. Grey-Turner, G.: A Giant Gallstone Impacted in the Colon and Causing Acute Obstruction, Brit. J. Surg. **20**: 26, 1932.
8. Holz, E.: Zur Frage des Gallensteinileus, Arch. klin. Chir. **155**: 166, 1929.
9. Illyés, Z., and Gerlei, F.: Durch in das Duodenum perforierten Gallenstein bedingte Pylorusstenose, Zentralbl. Chir. **81**: 2290, 1956.
10. Lehr, P.: Ein Fall von rezidivierendem Gallenstein-Ileus, Ztschr. ges. inn. Med. **11**: 415, 1956.
11. Mossimann, R.: Iléus biliaire, Helvet. chir. acta **23**: 496, 1956.
12. Nemir, P.: Gallstone Ileus, Surg. Gynec. & Obst. **94**: 49, 1952.
13. Niederle, B.: Uzávěr vrátníku žlučovými kameny, Sbor. pathofys. tráv. výž. **5**: 93, 1951.
14. Noskin, E. A., and Tannenbaum, W. J.: Recurrent Gallstone Ileus, SURGERY **31**: 599, 1952.
15. Paschold, K.: Zur Klinik des Gallenstein-Ileus und seiner Rezidive, Zentralbl. Chir. **81**: 2284, 1956.
16. Quodbach, K.: Gesichtspunkte zur Erkennung und Behandlung des Gallensteinileus, Zentralbl. Chir. **80**: 584, 1955.
17. Samain, A.: Le pronostic de l'iléus biliaire, Acta gastroenter. Belg. **14**: 556, 1951.
18. Schulte, F.: Über rezidivierenden Gallensteinileus, Zentralbl. Chir. **79**: 2069, 1954.
19. Výborný, J.: Ileus biliaris, Prakt. lék. **32**: 82, 1952.
20. Wangensteen, O. H.: Intestinal Obstructions, Springfield, Ill., 1949, Charles C Thomas.

WILMS'S TUMOR: AN EVALUATION OF PROGNOSIS AND TREATMENT

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MANY factors should be considered in assessing the effectiveness of the treatment of Wilms's tumor. The age of the patient, the promptness of diagnosis, and the concomitant presence of signs and symptoms may be almost as important as the specific type of therapy. In addition, the late complications resulting from certain kinds of therapy warrant attention. This report is based on a study of all the patients with Wilms's tumor admitted to the University of Rochester Medical Center during the past 30 years. Since most of the survival cases have been followed over a long period of time, it has been possible to evaluate these various factors.

Some of the pertinent reports which have led to current therapy are briefly reviewed here. With surgery alone as treatment Ladd[11] reported a 32 per cent survival rate for cases at the Boston Children's Hospital during the 1930's. In 1945 Dean[5] reported a 25 per cent survival rate in a series treated by x-ray alone.

In 1941 Ladd and White[12] called attention to the importance of the age of the patient when considering results. They noted the survival rate to be much higher among children in the first 12 months of life. Many others have confirmed this finding. In 1953 Gross[8] reported an 80 per cent survival rate using surgery and postoperative irradiation in infants 12 months of age or younger. With the same therapy in children over 12 months of age, however, his survival rate was only 43 per cent.

In 1946 Nesbitt and Adams[15] reported upon 12 nephrectomized patients with Wilms's tumor, only 2 of whom received irradiation; of these, 7 survived for a 58.7 per cent cure rate.

In 1956 Ng and Low-Beer[17] reported on 19 operated cases, some with and some without irradiation; here there were 14 survivals, for a 73.6 per cent survival rate. All of their survival cases were 19 months of age or younger. Of the 4 children treated by surgery alone 3 survived. Recently, Lattimer[13] reported 4 survivals in 5 patients who underwent nephrectomy only.

METHOD

This report covers 18 patients with a tissue diagnosis of Wilms's tumor. Because of the difference in prognosis, the children under 18 months of age have been compared separately.

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Since signs and symptoms are often considered a late finding with Wilms's tumor, the incidence of signs and symptoms has been compared to survival.

We have not used the usual 18-month post-therapy period as a criterion for survival because this criterion is meaningless in the older age group. Some of the patients succumbed to their tumor after 18 months' survival. Instead, we have used a method, first suggested by Collins,[4] which uses a sliding-scale period of risk. Essentially, this period of risk is based on the fact that the date of origin of the tumor cannot be earlier than the patient's conception; therefore, if the tumor recurs at a similar rate of growth, it should again be clinically evident within a similar period of time. For example, a patient whose tumor is first discovered at 2 years of age would have a period of risk equal to the patient's age (24 months) plus the gestational period (9 months). This would make a total period of 33 months for the tumor again to become evident. In the 206 cases reported by Collins[4] and in our own 18 cases no patient has passed this sliding-scale period of risk and subsequently either developed a clinical recurrence or succumbed to his tumor.

Since most of our patients have been followed for a long period of time, an unusual opportunity was afforded to observe the incidence of late sequelae associated with irradiation, and this factor has also been evaluated.

RESULTS

Table I compares survival rate with number of symptoms. Among patients with two or more symptoms, the mortality spiraled.

Table II presents the over-all results, with a 55 per cent survival rate. If the 3 patients treated by irradiation alone are excluded, the survival rate for the remaining 15 patients (that is, those having surgery and postoperative irradiation) is 66 per cent.

TABLE I. SIGNS AND SYMPTOMS IN RELATION TO SURVIVAL WITH WILMS'S TUMOR

SIGNS AND SYMPTOMS	TOTAL	ALIVE	DEAD	PER CENT SURVIVAL
Mass	18	9	9	50
Pain	10	3	7	30
Fever	13	4	9	31
Hematuria	6	2	4	33
Tarry bowel movements	2	0	2	0
Symptoms other than mass:				
One symptom	5	5	0	100
Two symptoms	7	2	5	29
Three symptoms	4	0	4	0

TABLE II. RESULTS OF TREATMENT FOR WILMS'S TUMOR

TREATMENT	TOTAL	ALIVE	DEAD	PER CENT SURVIVAL
Preoperative irradiation, plus nephrectomy, plus postoperative irradiation	3	2	1	66
Nephrectomy, plus postoperative irradiation	12	8	4	66
Irradiation alone (due to far-advanced metastasis)	3	0	3	0
Total	18	10	8	55

Table III shows the results of treatment among children 18 months of age or younger. There were 9 such patients and all survived.

TABLE III. RESULTS OF TREATMENT OF WILMS'S TUMOR UNDER 18 MONTHS OF AGE

TREATMENT	TOTAL	ALIVE	DEAD	PER CENT SURVIVAL
Preoperative irradiation, plus nephrectomy, plus postoperative irradiation	2	2	0	100
Nephrectomy, plus postoperative irradiation	7	7	0	100
Total	9	9	0	100

Table IV illustrates the late bony complications associated with irradiation. The amount of irradiation used in all of these cases varied between 2,500 and 4,000 r. One patient had only a mild scoliosis. Of 3 patients with marked scoliosis and marked kyphosis, 2 had appreciable shortening of one limb. Hypoplasia of the ilium was noted in 2 children. One child had developed severe scoliosis extending from L_1 to L_3 in less than 3 years after treatment.

TABLE IV. EARLY AND LATE MORBIDITY

	TOTAL	ALIVE	DEAD	PER CENT SURVIVAL
Gibbus with scoliosis	4	4	0	100
Scoliosis alone	1	1	0	100
Ilium hypoplasia	2	2	0	100
Transient leukopenia	5	1	4	20
Suspected metastatic lung masses (secondarily irradiated)	2	2	0	100

Fig. 1 shows the validity of using a period of risk equal to the age of the patient at the time of diagnosis plus 9 months (gestation period). The vertical line represents the age at diagnosis, the horizontal line the age at the last follow-up. All recurrences and deaths were evident within the period of risk, and no recurrences or deaths have occurred beyond the predicted period of risk.

DISCUSSION

The incidence of signs and symptoms is significantly related to prognosis. Tarry stools were noted in 2 of our patients. This finding has not been previously observed in connection with Wilms's tumor, although Ng and Low-Beer[17] reported purpura as one of the presenting signs.

In one case the tumor of a patient in this series was diagnosed when the patient was 10 days of age; undoubtedly, it existed prior to birth. Wells[19] has reported 5 patients in whom a tumor was present at birth. Potter[18] has noted in the kidneys of stillborn fetuses the presence of multiple areas of nephroblastic tissue microscopically similar to Wilms's. Gaulin[7] has reported corresponding tumors in identical twins. The bilateral incidence of Wilms's tumor has been variously estimated at from 3 to 7 per cent. Maslow[14] has described 3 cases in the same family, with a possible fourth. Fitzgerald and

Hardin[6] have noted Wilms's tumor in the father and 2 children of the same family. The mother of one of our patients died of a sarcoma of the kidney. All these findings tend to substantiate the probability that Wilms's tumor is hereditary and has its inception in utero.

As in other reports on Wilms's tumor, our series contains a small number of patients. It serves, however, to pose certain questions. The first concerns the importance of age. Both in this report and in others one is impressed with the way the prognosis hinges on whether or not the diagnosis is made and treatment is begun before 18 months of age. All 9 of our children under 18 months of age survived, whereas only one of the remaining 9 over 18 months of age survived. Similarly, all of the "cures" in Ng and Low-Beer's[17] series were 19 months of age or younger. Gross's[8] latest series showed a 43 per cent survival for children over 12 months of age. It is apparent that all reports on Wilms's tumor should segregate the very young patients.

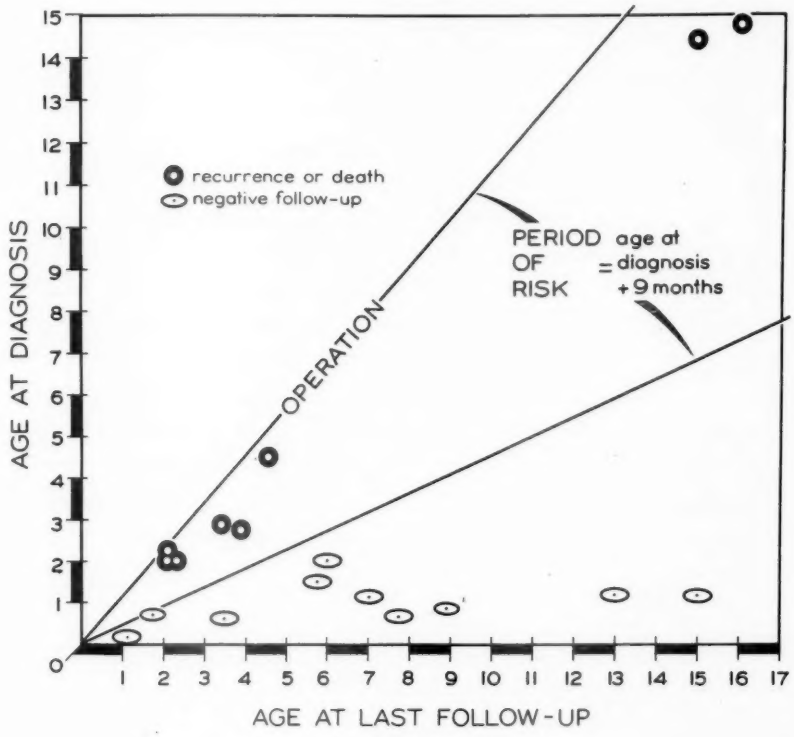
recurrence or death
negative follow-up
PERIOD OF RISK
age at diagnosis +9 months
OPERATION
AGE AT DIAGNOSIS
AGE AT LAST FOLLOW-UP
0 1 2 3 4 5 6 7 8 9 10 11 12 13 14 15
1 2 3 4 5 6 7 8 9 10 11 12 13 14 15 16 17

Fig. 1.

The second question concerns the time period that should be used to designate a patient as a survivor. Collins[4] has made observations on the growth rate of Wilms's tumor by studying, serially, the growth rate of pulmonary nodules of Wilms's tumor. From these observations he has estimated and correlated a quantitative rate of growth, suggesting a uniform growth rate for Wilms's tumor. On this basis he uses the simplest concept for the multiplication of cancer cells. He begins with a single cell which initiates a series of doublings (2-4-8 and so on) to establish a colony of tumor cells. From this he

calculates that a single cell of 10 micrometers would require 20 doublings to be equal to 1 ml. in diameter and another ten doublings to be equal to 1 cm. With another ten doublings (still at the same rate of growth) the tumor would be 1 Kg. in weight. Applied to Wilms's tumor, these calculations indicate that no tumor can be older than the patient's age plus 9 months (gestation period). The sliding-scale period of risk which we have used is thus consistent not only with the apparently congenital nature of Wilms's tumor and the important factor of age but also with the only quantitative study on the tumor's rate of growth.

The third question concerns the validity of the routine use of x-ray to the renal fossa. It is known that 800 r. will significantly affect epiphyseal growth. During the past 15 years, 2,000 to 4,000 r. have been used for the treatment of the renal fossa, and it is not surprising that 6 of the 10 cures in this series had bony sequelae.

Gross and Neuhauser[9] have emphasized the bony changes following irradiation for Wilms's tumor. Johnson[10] has noted the rarity of local recurrences in the renal fossa, even when the lungs are widely studded with tumor. Critical analyses of the reports of Nesbitt and Adams[15] and of Ng and Low-Beer[17] suggest that surgery alone carries an impressive survival rate. Although these series are small, they do, together with ours, raise the question whether individualization of therapy might not have a place in the treatment of Wilms's tumor during the first 2 years of life. Much of the increased survival rate which started with the reports of the 1940's was credited to the adjunct of irradiation. There has thus been a tendency to overlook other important contributions made at that time. For example, Ladd and White[12] first called attention to the importance of age in relation to prognosis, with a resultant segregation of the younger age group. Survival comparisons then were still being made to the sparse reports of the 1930's, when it was not yet recognized that the size of the tumor had no relationship to its curability. Surgeons were often hesitant to operate, and there was much delay and handling of the tumor. Chemotherapy and improved anesthesia were important contributions that encouraged surgeons to operate earlier, and operative mortality was reduced.

SUMMARY

The experience at the University of Rochester Medical Center with Wilms's tumor is summarized here and evaluated with regard to the following important factors: the age of the patient at time of diagnosis; the presence of multiple signs and symptoms; the incidence of late bony sequelae to irradiation; the method used in determining a patient a survivor; the results after long-term follow-up.

As in other reports, the prognosis in children under 18 months of age is much better. There was a 100 per cent survival rate for the 9 patients who were 18 months of age or younger, whereas there was only an 11 per cent survival rate for those over 18 months.

Among patients with two or more symptoms the mortality increased greatly.

Among the survival cases there was a high incidence of late skeletal changes resulting from irradiation: gibbus deformities of the spine, scoliosis, and hypoplasia of the ilium.

As a criterion for survival, the usefulness of a sliding-scale period of risk, first described by Collins,[4] is demonstrated. Much evidence indicates that Wilms's tumor is present before birth. If the tumor recurs at a similar rate of growth, it should again be clinically evident within a period of time not to exceed the age of the patient at time of original diagnosis and treatment plus 9 months (gestation period).

As long as surgery is included, the survival rate for Wilms's tumor in patients under 18 months of age is high regardless of type of therapy. In this age group there may be some justification for individualizing therapy and avoiding irradiation in an effort to eliminate late bony deformities.

REFERENCES

1. Abeshouse, B. S.: The Management of Wilms's Tumor as Determined by National Survey and Review of the Literature, J. Urol. **77**: 792, 1957.
2. Collins, V. P.: The Treatment of Wilms's Tumor, Cancer **11**: 89, 1958.
3. Collins, V. P.: Wilms's Tumor: Its Behavior and Prognosis, J. Louisiana M. Soc. **107**: 474, 1955.
4. Collins, V. P., Loeffler, R. K., and Tivey, H.: Observations on the Growth Rate of Human Tumors, Am. J. Roentgenol. **76**: 988, 1956.
5. Dean, A. L.: Wilms's Tumor, New York J. Med. **45**: 1213, 1945.
6. Fitzgerald, W. I., and Hardin, H. C., Jr.: Bilateral Wilms's Tumor in a Wilms's Tumor Family Case Report, J. Urol. **73**: 468, 1955.
7. Gaulin, E.: Simultaneous Wilms's Tumor in Identical Twins, J. Urol. **66**: 547, 1951.
8. Gross, R. E.: Surgery of Infancy and Childhood, Philadelphia, 1953, W. B. Saunders Co., p. 558.
9. Gross, R. E., and Neuhauser, E. B. O.: Treatment of Mixed Tumors in Childhood, Pediatrics **6**: 843, 1950.
10. Johnson, S. H., and Marshall, M.: Primary Kidney Tumors in Children, J. Urol. **74**: 707, 1955.
11. Ladd, W. E.: Embryoma of the Kidney (Wilms's Tumor), Ann. Surg. **108**: 885, 1938.
12. Ladd, W. E., and White, R. R.: Embryoma of the Kidney, J. A. M. A. **17**: 1858, 1941.
13. Lattimer, J. K., Melicow, Meyer, M., and Uson, A. C.: Wilms's Tumor: Improved Results With Modern Therapy, New York J. Med. **59**: 415, 1959.
14. Maslow, I. A.: Wilms's Tumor: Report of Three Cases and a Possible Fourth One in the Same Family, J. Urol. **43**: 75, 1940.
15. Nesbitt, R. M., and Adams, F. M.: Wilms's Tumor. A Review of Sixteen Cases, J. Pediat. **29**: 295, 1946.
16. Neuhauser, E. B. D., Wittenberg, M. H., Berman, C. Z., and Cohen, J.: Irradiation Effects of Roentgen Therapy on the Growing Spine, Radiology **59**: 637, 1952.
17. Ng, Elmer, and Low-Beer, B. V. A.: The Treatment of Wilms's Tumor, J. Pediat. **48**: 763, 1956.
18. Potter, E. L.: Pathology of the Fetus and Newborn, Chicago, 1952, The Year Book Publishers, Inc., p. 170.
19. Wells, H. G.: Occurrence and Significance of Congenital Malignant Neoplasms, Arch. Path. **30**: 535, 1940.

LATE POSTOPERATIVE "HEMOBILIA" TREATED WITH PERIPHERAL LIGATION OF THE HEPATIC ARTERY

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THIS paper is a report on a patient in whom profuse hemorrhage from the intrahepatic bile ducts developed one month after cholecystectomy and choledochotomy. The hemorrhage was arrested by peripheral ligation of the hepatic artery.

CASE REPORT

A woman, aged 64, with a 4-year history of biliary tract disease, which had repeatedly given rise to jaundice and fever, was subjected to cholecystectomy and choledocholithotomy in June, 1957. The operation revealed stones in the cystic duct and the gall bladder, and a small stone was removed from the common duct by means of a scoop. The common duct was probed by bougies. The immediate postoperative course was uneventful. Four weeks after the operation the patient had a large hematemesis, which stopped after blood transfusion, but recurred on six occasions at short intervals. In August, 1957, the patient was re-admitted with a fresh hematemesis and melena, in mild shock. The patient was at once treated with blood transfusions, following which the hematemesis stopped.

Roentgenograms revealed a sliding hernia of the esophageal hiatus, a slightly deformed duodenal bulb, suggestive of ulcer, and a duodenal diverticulum.

Even though esophagoscopy did not reveal any peptic ulcer in the hiatal hernia, the hemorrhage was suspected to originate from this, for which reason transthoracic herniotomy on the orange-sized sliding hernia was performed. Two weeks after the second operation another large hematemesis occurred. As this persisted, in spite of repeated transfusions, a bleeding duodenal ulcer was suspected and a third operation was performed.

This operation disclosed that the stomach and small intestine were filled with blood, but the stomach and duodenum did not show any ulcerations. On the other hand, the common bile duct was distended to the thickness of a thumb and was filled with blood. Duodenotomy revealed fresh, pulsating bleeding through the papilla of Vater. Sphincterotomy was then performed, because it was suspected that the bleeding originated from the sphincteric region, since the pancreatic tissue in this region seemed to be indurated, but the bleeding proved to be coming from a higher level. Through the choledochotomy, established in the region of the cystic duct, it was seen that the bleeding came from the intrahepatic bile ducts. As the condition of the patient became very critical, rapid hemostasis was imperative, and, as it was not possible to arrest the bleeding by other methods, we found it vitally necessary to perform ligation of the hepatic artery peripheral to the origin of the pancreatoduodenal artery, following which the hemorrhage stopped. Palpation did not reveal any tumors of the liver, the surface of which appeared to be normal.

Postoperatively, the patient was given penicillin, 2 million units twice daily for 25 days, and streptomycin, 1 Gm. daily for 11 days. She was discharged in a state of well-being 32 days after the last operation.

The results of laboratory examinations during the postoperative period were: thymol turbidity, 0.02, 0.07; serum bilirubin, 1.1, 0.3 mg./100 ml.; alkaline serum phosphatase,

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10.2, 7.9, 9.7 units; total cholesterol in serum, 130, 178, 195 mg./100 ml.; zinc sulfate turbidity test, 8, 0.9 unit; serum albumin, 2.31, 1.97, 2.62 Gm./100 ml. with normal total protein; SGO transaminase, 2.8, 0.6 unit; SGP transaminase, 5.5, 0.2, 0.7 unit.

Thirteen months after the ligation of the hepatic artery the patient was admitted with a ventral hernia in the operative scar. In the meantime she had been perfectly well and had not had hematemesis or melena.

Ventral herniotomy was performed. During the operation the liver was inspected. It seemed to be slightly smaller than normal, but was otherwise of normal appearance. A biopsy specimen showed slight degeneration of the intercellular connective tissue and of the parenchyma of the liver.

Abdominal aortography showed good filling of the celiac, gastric, and splenic arteries, but no inflow into the hepatic artery.

DISCUSSION

In 1948, Sandblom[6] suggested the term "traumatic hemobilia" for hemorrhages through the common bile duct occurring after blunt trauma to the liver region. It will also be reasonable to use the term hemobilia for postoperative hemorrhages through the common duct, which must be presumed to be far less common than traumatic hemobilia.

Whereas several cases have been reported of late postoperative hemorrhage around the intrahepatic bile ducts, due either to lesions of the hepatic tissue at the gall-bladder site[4] or to a traumatic aneurysm of the hepatic artery,[3] we have been able to trace only 1 case of postoperative hemobilia in the literature available to us.[1] In this case, a fatal hemorrhage through the common bile duct occurred a few weeks after gastric resection, at which time choledochotomy with drainage had also been performed. Autopsy revealed that the hemorrhage originated from an erosion on the common duct opposite to a branch of the pancreatoduodenal artery. This artery had probably been damaged by a suture.

In our own case, it was assumed that the hemobilia was referable to a lesion of the intrahepatic bile ducts inflicted during the choledocholithotomy, by which a secondary lesion of a branch of the hepatic artery had occurred. The possibility that the hemorrhage should have been caused by a tumor can presumably be excluded, since the patient was well for 13 months after the last operation. Obviously, it cannot be ruled out that the hemorrhage originated from an intrahepatic aneurysm of the hepatic artery, but it has never been reported that such aneurysms may rupture into the bile ducts. As already stated, the bleeding was arrested by the ligation of the hepatic artery.

As far as we know, this form of treatment has never been used before, but the result was good and, in later studies of the patient, only slight histologic changes in the liver tissue could be demonstrated, while the conventional liver function tests did not reveal any abnormalities.

It has been reported that experimental ligation of the hepatic artery does not give rise to complications in monkeys[2] or dogs[5]; in the latter animal, large doses of antibiotics were given to prevent septic infarction of the liver, which may readily occur when the oxygen supply is reduced. For the same reason, large amounts of penicillin and streptomycin were administered to our patient, who did not afterward reveal any signs of infection of the liver.

However, as long as closer studies on ligation of the hepatic artery in man have not been performed, this form of treatment should presumably be used only in cases in which no other therapeutic possibilities are open.

SUMMARY

A case is reported in which postoperative hemobilia was arrested by ligation of the hepatic artery.

REFERENCES

1. Campbell, D. H.: Intracholedochal Hemorrhage, Ann. Surg. **141**: 125, 1955.
2. Child, C. G.: The Hepatic Circulation and Portal Hypertension, Philadelphia and London, 1954, W. B. Saunders Company, p. 196.
3. Grant, J. L., Fitts, W. T., and Ravdin, I. S.: Aneurysm of the Hepatic Artery, Surg. Gynec. & Obst. **91**: 527, 1950.
4. Hart, D.: Biliary Tract Hemorrhage (Discussion), Ann. Surg. **131**: 790, 1950.
5. Horvath, S. M., Farrand, E. A., and Larsen, R.: Effect of Hepatic Arterial Ligation on Hepatic Blood Flow and Related Metabolic Function, Ann. Surg. **74**: 565, 1957.
6. Sandblom, P.: Hemorrhage Into the Biliary Tract Following Trauma—"Traumatic Hemobilia," SURGERY **24**: 571, 1948.

THE EFFECT OF TEMPERATURE ON INTESTINAL MOTILITY

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THE slowing of metabolic processes in animal tissues by cooling them below normothermic temperatures is well recognized. Surgeons have applied this phenomenon advantageously, using hypothermia to depress the metabolic requirements of vital organs and thus gaining time for more careful and extended operations. Recent observations reported from this laboratory have shown that local and systemic hypothermia slow the secretory activity of the stomach and bowel[2, 3] and reduce the blood flow in these organs.[1] This paper presents data showing the effect of alterations of body temperature and local bowel temperature upon bowel activity.

SYSTEMIC HYPOTHERMIA

Methods.—Bowel motility was studied in bullfrogs, rats, and rabbits by following the progress of a barium meal with serial x-ray pictures. All the animals were normothermic (frogs 25° C.) when the barium meal was given. By means of a suitable stomach tube, bullfrogs (Rana catesbieana) received 10 ml., rats 5 ml., and rabbits 50 ml. of a watery barium solution. Control animals were maintained at normothermic temperatures (frogs 25° C.) while those in the experimental group, after being wrapped in towels, were immersed briefly in ice water to induce systemic hypothermia. Frogs, being poikilothermic, were kept at various temperatures by adjusting the temperature of their environment. Hypothermic animals were maintained within narrow temperature ranges: rabbits at 30° to 33° C.; rats in two groups at different temperatures, one at 25° to 29° C. and the other at 30° to 33° C.; and frogs at 7°, 15°, 20°, and 27° C.

Results.—The results are depicted by the accompanying photographs of a series of x-ray films which show the progress of a barium meal in the normothermic and hypothermic animals.

Frogs: Fig. 1, Temperatures 7°, 15°, 20°, and 27° C.

Two groups, each comprised of 4 frogs, were studied for periods of up to 132 hours following administration of the barium meal. The variation in the progress of the meal is clearly evident after 36 hours and the figures amply

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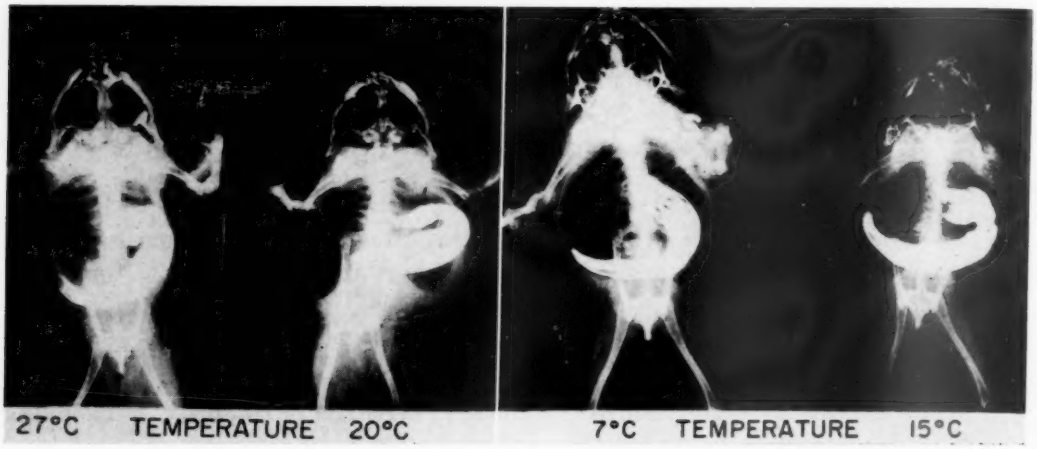
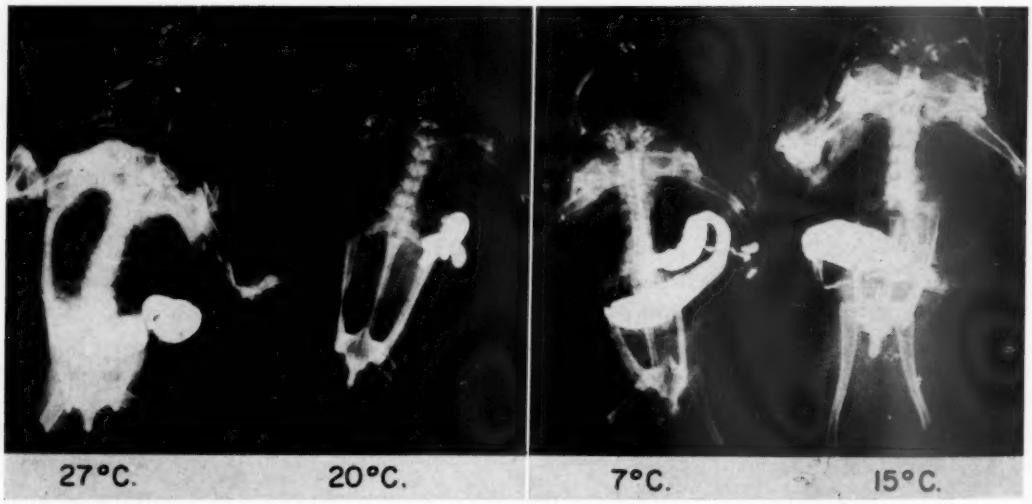
demonstrate the slowing of bowel motility in the colder animals. Later films (not illustrated here) after 57 hours show that frogs at 27° and 20° C. have excreted almost all the barium. However, in frogs kept at 15° and 7° C. the barium meal was completely retained within the bowel for as long as 132 hours.



A. *B.*

Immediate.



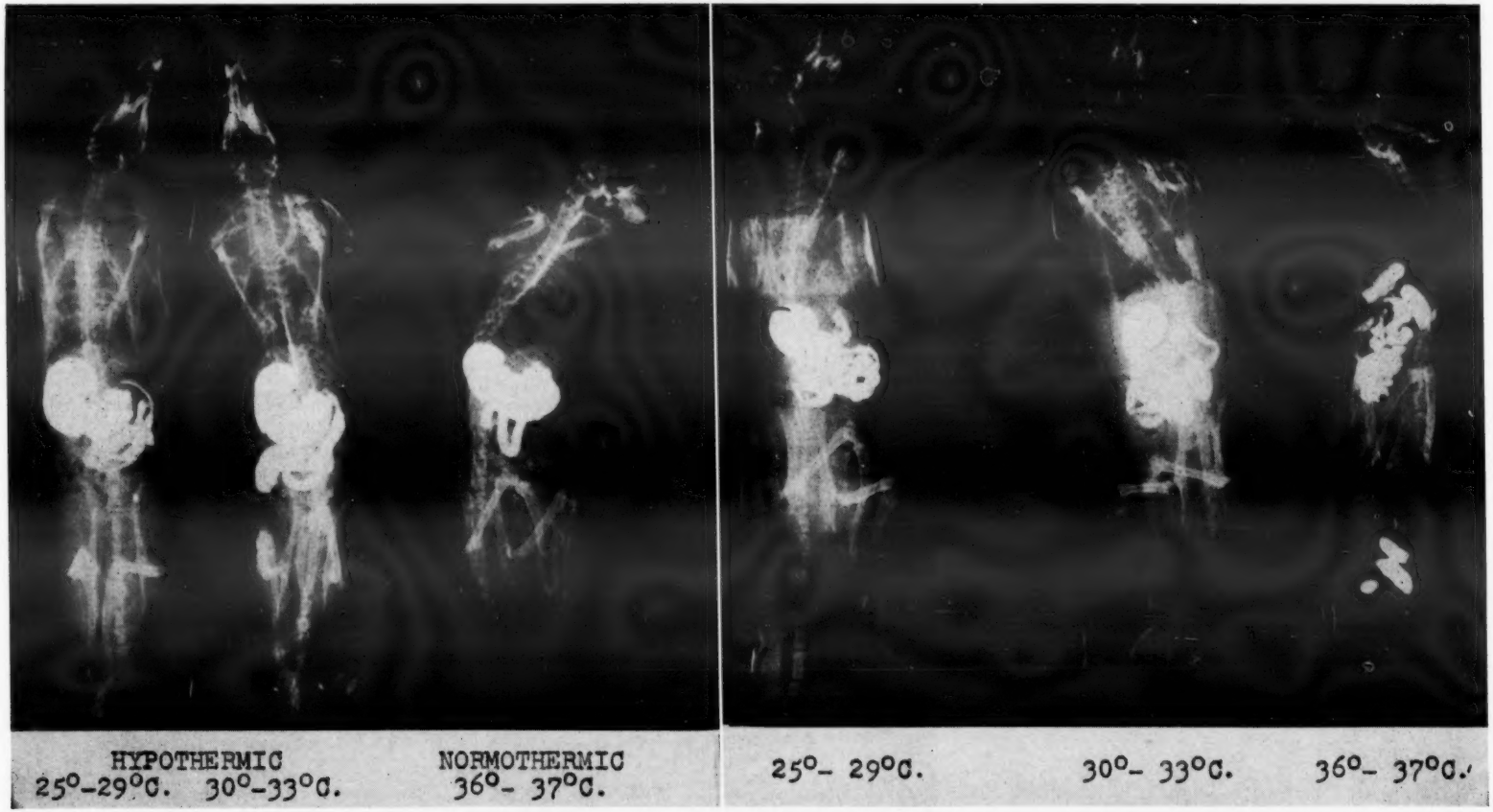
C. *D.*

36 hours.

Fig. 1.—Frogs. In the warmer animals the barium meal is in the distal regions of the bowel after 36 hours but in the hypothermic animals it is largely retained in the stomach after the same period of time.

Rats: Fig. 2, Temperatures 25° to 29°, 30° to 33°, and 36° to 37° C.

Serial x-ray films were taken in two groups of 3 rats during an experimental period of 27 hours. The illustrations show the marked difference in the rate of passage of barium in the normothermic and hypothermic animals. The normothermic animal had a barium stool in 4 hours. The rapid transit time may reflect stimulation of the bowel by the barium bolus. Failure of the hypothermic animals to respond similarly when equal volumes of barium were



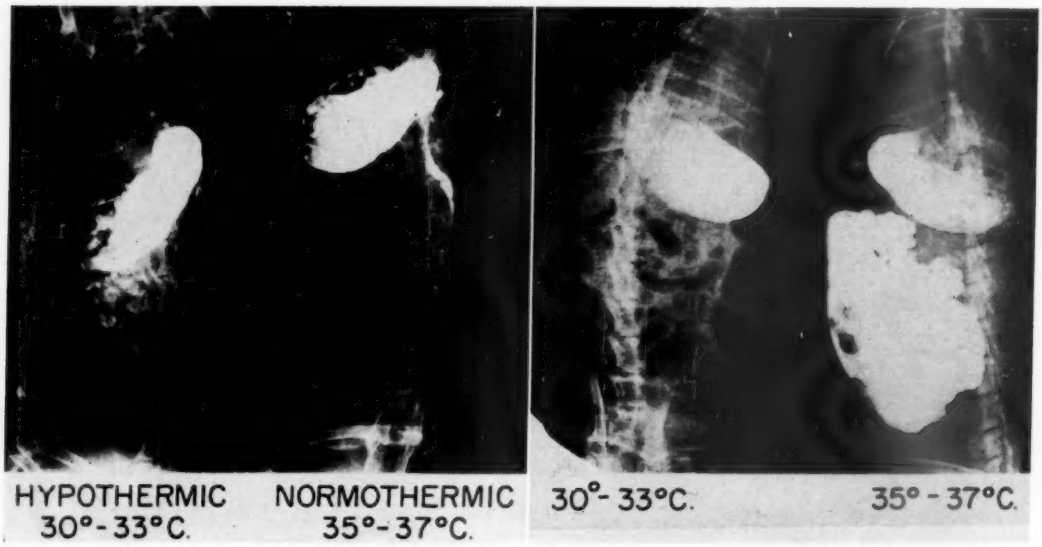
Immediate. 10 hours.

Fig. 2.—Rats. The normothermic animal passed barium stool after 4 hours. The hypothermic animal retained most of the barium in the stomach and proximal small bowel.

given further serves to illustrate the suppressive effect of cold. A later film, not shown here, taken after 27 hours, shows a trace of barium remaining in the colon of the normothermic rat. After the same interval, the hypothermic animals in both temperature ranges still had barium within the stomach or in the small bowel; none had reached the colon.

Rabbits: Fig. 3, Temperatures 30° to 33° C. and 35° to 37° C.

Two groups of 2 rabbits each were followed over a period of 25 hours. In Fig. 3 the retarding effect of cold on the passage of the barium meal is again well illustrated. Although in both warm and cold animals a small amount of barium passed from the stomach into the duodenum immediately following injection, complete gastric retention was maintained thereafter for up to 10 hours in the hypothermic animals. Other films, not illustrated here, show that after 25 hours the stomachs of animals at 30° to 33° C. were still well outlined; some barium, however, had passed down the bowel as far as the colon. Following a similar time period, the normothermic animal had barium only in the distal bowel and colon and had excreted much of it.



Immediate. 4 hours.

Fig. 3.—Rabbits. After 10 hours most of the barium in the normothermic rabbit had passed from the stomach into the bowel. The hypothermic rabbit retained all of the barium within the stomach.

LOCAL HYPOTHERMIA

Methods.—The effect of local hypothermia on bowel motility was investigated in rabbits. The animals were anesthetized lightly with intravenous sodium pentobarbital. The abdomen was opened and a loop of jejunum was exteriorized. A small polyethylene balloon, 6 by 10 mm., filled with distilled water and connected to a low-pressure transducer was used to record pressure changes within the bowel lumen. Rubber balloons, diaphragms, and open-tipped catheters failed to demonstrate consistent bowel activity. It is conceivable therefore that the balloon used was of large enough diameter to stimulate

activity of itself. The attenuator was set to record 0.5 mm. Hg per millimeter of graph paper and the speed of the paper was 0.25 mm. per second. The loop was surrounded by plastic bags through which water could be circulated

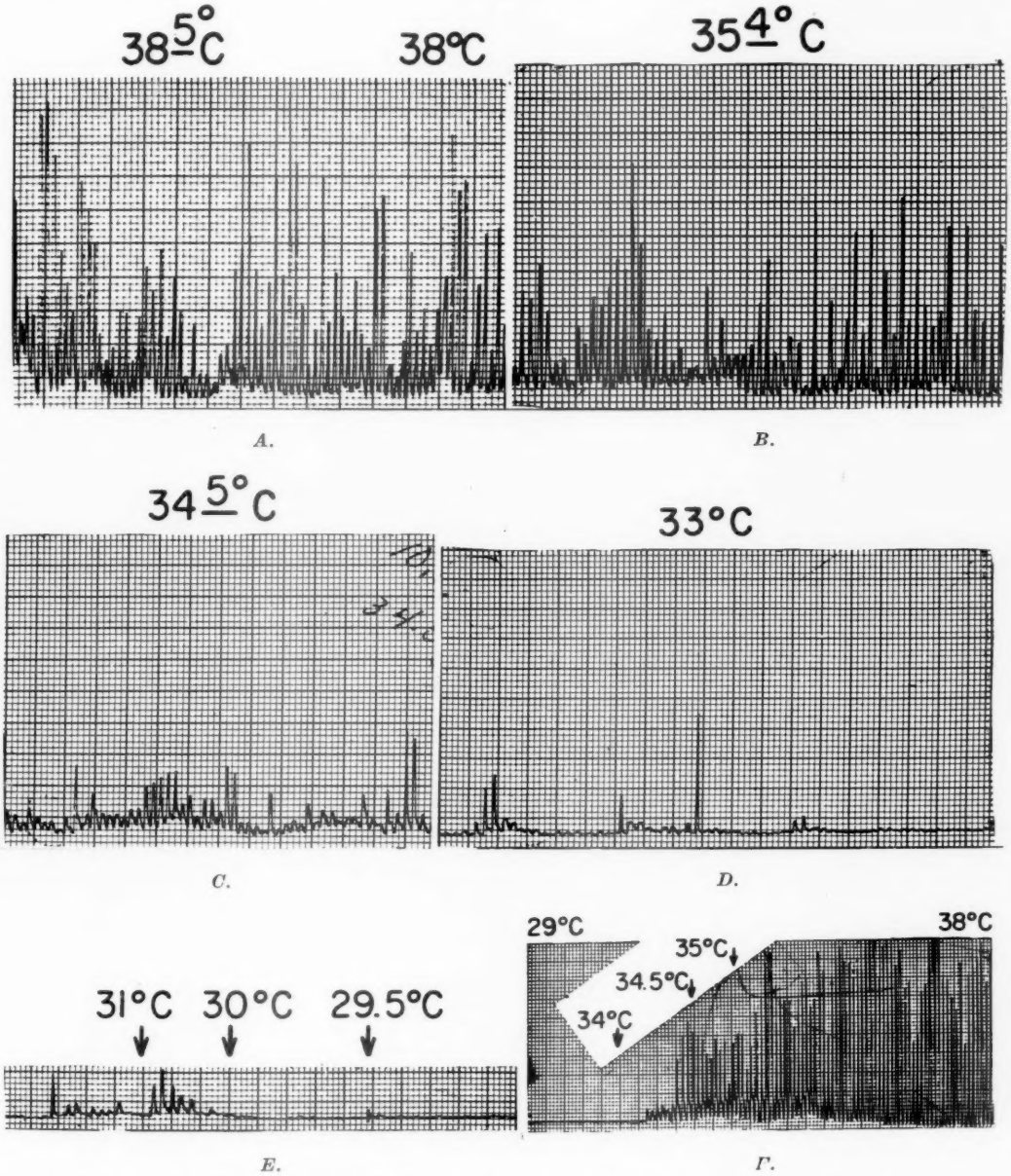
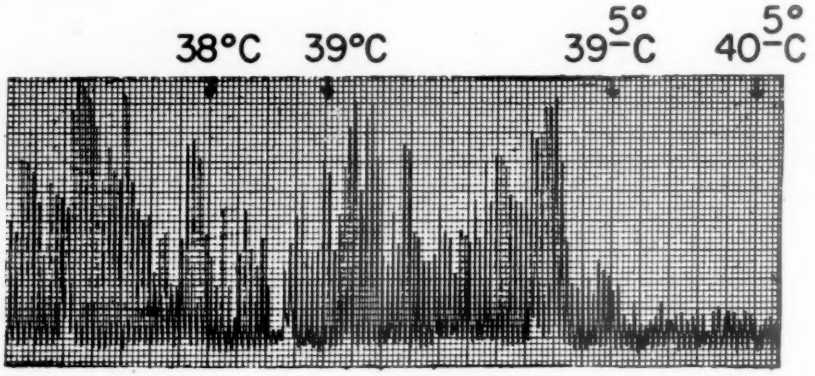


Fig. 4.—The marked decrease in bowel motility is easily observed in these tracings.

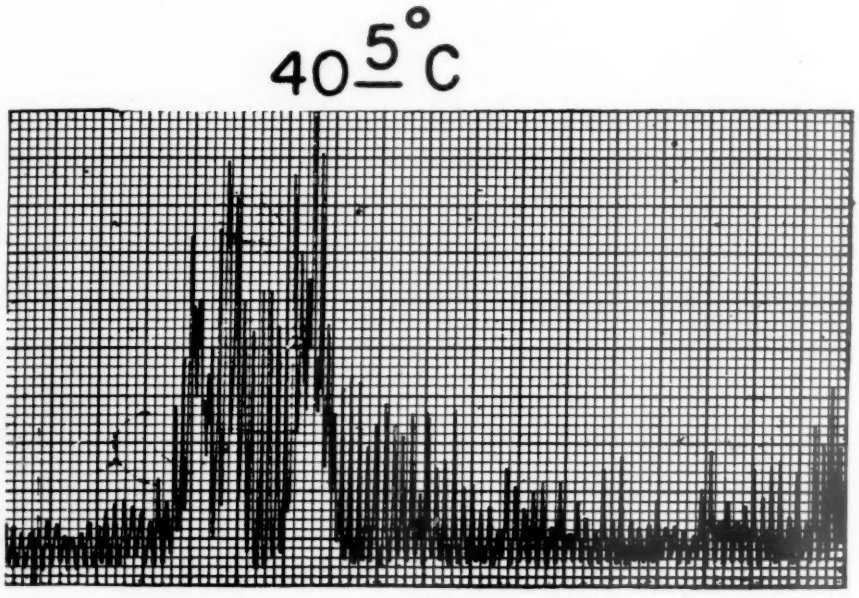
from a nearby constant temperature bath. The bags were arranged in such a way as to place only slight pressure on the bowel. A thermocouple was placed within the bowel lumen to record the temperatures.

Results.—Figs. 4 and 5. The sequences of figures show typical recordings obtained as the temperature of the bowel was slowly reduced from 38° to 29.5°

C. At 38° C. bowel contractions occur every 4 to 5 seconds in a uniform fashion and represent Type I or segmenting activity. The pressure at the peak of contraction varies considerably but is generally between 20 and 30 cm. H_2O. Bowel activity is definitely seen to decrease both in amplitude and frequency as the temperature is reduced, until at 30° C. it essentially stops. A rapid reduction in temperature of the bowel wall will cause a momentary burst of activity but this shortly subsides and a general diminution in activity as described previously again becomes evident.



A.



B.

Fig. 5.—Hyperthermia (over 39.5° C.) produces a decrease in the amplitude of contraction and occasional bursts of activity (Type II) are observed every 10 to 15 minutes.

The second series of tracings demonstrate the effect of gradually increasing the temperature of the bowel wall. In this record there is no change in activity up to 39° C. Above 40° C. the amplitude of the recorded waves

diminishes to 4 to 5 cm. H_2O; however, the frequency of contraction is unchanged. Superimposed on the Type I activity are Type II waves that occur 5 to 10 minutes apart.

DISCUSSION

The depression of bowel activity by hypothermia is constant throughout these experiments and is in keeping with the accepted concept that cooling reduces the rate of animal metabolism. Local hypothermia has also been found to reduce the rate of secretion in bowel and stomach and to slow markedly the absorption of strychnine from the bowel lumen. This depression of activity may also reflect a decreased blood flow to the segment. The intravenous injection of parasympathomimetic drugs such as pilocarpine, neostigmine, Mecholyl, and Urecholine produced no increase in bowel activity under conditions of systemic or local hypothermia. Ilopan (pantothenyl alcohol) and serotonin also failed to increase activity. Hyperthermia, although appearing to have little effect on bowel activity at temperatures between 38° and 40° C., produced a significant decrease in the amplitude of the recordings at temperatures above this level.

CONCLUSIONS

1. Hypothermia, local or systemic, reduced both the amplitude and frequency of bowel contractions until at about 30° C. motility essentially ceased.

2. Hyperthermia does not appear to change bowel activity at temperatures a degree or two above 38° C. However, when the temperature of the bowel wall is raised above 40° C., there is a decrease in the amplitude of the recorded pressure waves but little change in the frequency of contraction. Type II contractions occurring every 10 to 15 minutes are superimposed on the Type I activity at elevated temperatures.

REFERENCES

1. Salmon, P. A., Griffen, W. O., Jr., Paterson, J. R. S., Fattah, F., and Wangensteen, O. H.: Effect of Intragastric Temperature Changes Upon Gastric Blood Flow, Proc. Soc. Exper. Biol. & Med. In press.
2. Salmon, P. A., Griffen, W. O., Jr., Root, H. D., Jenson, C. B., Imamoglu, K., and Wangensteen, O. H.: Depression of Gastric Digestion and Blood Flow by Local Hypothermia: Clinical Application in the Control of Massive Upper Gastrointestinal Hemorrhage, Univ. Minnesota M. Bull. **30**: 200, 1959.
3. Salmon, P. A., Griffen, W. O., Jr., and Wangensteen, O. H.: Influence of Hypothermia on Secretory Activity of Rabbits' Appendix and on Closed Duodenal Loops, Proc. Soc. Exper. Biol. & Med. **101**: 150-152, 1959.

A NEW METHOD FOR ONE-STAGE HEPATECTOMY FOR DOGS

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ONE of the traditional methods for investigation of the function of various viscera has been by analysis of the consequences of removal of the organ or organs in question. Although this has generally been a simple matter technically, the extirpative approach to the problem of hepatic function in the dog has proved to be unusually troublesome. The anatomic basis for this is the close approximation of the subdiaphragmatic inferior vena cava to the liver. This relationship is so intimate that a segment of vena cava is resected in all popular methods of total hepatectomy and it is commonly thought that removal of the liver is not otherwise possible.[9] Employing this principle, it is then necessary to provide a mechanism for both portal and inferior caval venous return. This has been done with multiple-staged procedures designed to initially promote collateral venous return,[6, 8, 9] or in single-stage operations by the interposition of glass or plastic cannulae into the resected caval segment with drainage of the portal system into the vena cava more inferiorly.[2, 7, 10]

All presently employed methods of hepatectomy have serious disadvantages. The operative mortality is high. Multiple-staged methods require long intervals between operations, the final operation is bloody due to the presence of adhesions, and the state of caval and portal drainage is likely to be inadequate in the preparation finally obtained. The use of prosthetic cannulae in single-stage techniques introduces other hazards of air embolus, hemorrhage and clot formation, or defibrination in the cannula.

In this laboratory, considerable experience has accumulated with a single-stage total hepatectomy in which no prosthetic devices are used and in which the inferior vena cava is preserved. The operation has a mortality of less than 10 per cent. Maximum survival time compares favorably with any other method.

METHODS

Sixty mongrel dogs, weighing 10 to 30 kilograms were used. Until the day of surgery the animals were on standard kennel rations. In 56 cases, sodium pentobarbital anesthesia was used because of the requirements of the experiment for which hepatectomy was done. In 4 animals used for study of maximum

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survival time, ether anesthesia by face mask was employed. Endotracheal intubation was not necessary since the pleural cavity was never entered. Postoperatively, a glucose infusion was given at the rate of 0.3 to 1 Gm. per kilogram per hour. Isotonic saline was given at the rate of 4 to 8 c.c. per kilogram per hour. The intravenous infusions were delivered with a constant inferior pump to the dogs anesthetized with sodium pentobarbital, and intermittently with a syringe to the animals operated upon under ether anesthesia. In about half of the animals, blood transfusions of 200 to 300 c.c. were given, either several hours before operation or at the time of surgery. The animals studied for maximum survival were allowed complete freedom of a large room. Aside from the intravenous infusions and one postoperative dose of pencillin, no other therapy was given. Arterial and venous pressures were studied with inductance manometers which had a frequency response in excess of 30 cycles per second. The operation was done under clean rather than sterile conditions.

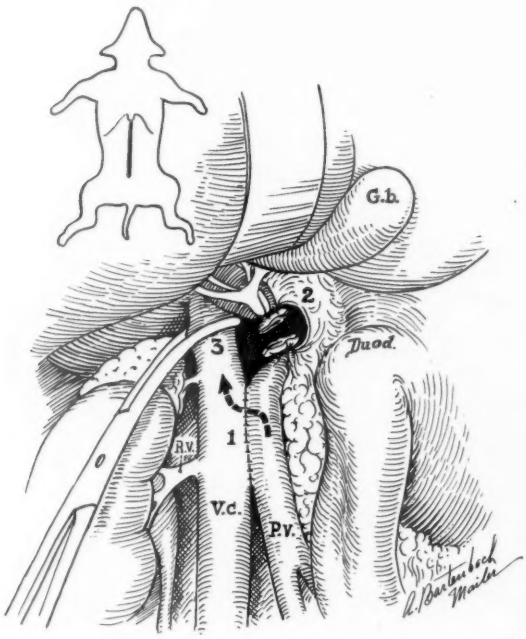

Fig. 1.—Total hepatectomy in dog. Portacaval anastomosis has been completed, and the portal triad ligated and divided. A noncrushing clamp has been applied to the inferior vena cava above the entrance of the adrenal veins.

DESCRIPTION OF TECHNIQUE

The abdomen is entered through a long upper midline incision (Fig. 1, inset). The inferior vena cava is looped with an umbilical tape, above the entrance of the adrenal veins, to facilitate subsequent manipulation. The portal triad is similarly encircled. A long (at least 1 cm.) side-to-side portacaval anastomosis is then performed, using modern vascular techniques, as previously described.[5, 11] Next the ligatures around the portal triad are tied, and the triad is cut (Fig. 1). The inferior vena cava is then occluded with a noncrushing clamp above the level of the adrenal veins (Fig. 1).

The hand is next placed over the dome of the liver and with gentle downward traction the mesenteries connecting the liver lobes to the diaphragm are cut. When this is completed a finger can be insinuated around the cava in the space between the diaphragm and the liver. The liver is then retracted inferiorly, and a noncrushing clamp is placed across the inferior vena cava between the dome of the liver and diaphragm (Fig. 2). The liver has now been completely devascularized, and the short segment of inferior vena cava into which the hepatic veins empty is trapped between the two noncrushing clamps.

It is now possible, in a bloodless field, to dissect the liver from the inferior vena cava. This is begun superiorly (Fig. 2). Viewed from below, the largest hepatic vein is located at 2 o'clock and is the first to be encountered (Fig. 2). It is often easiest to cut boldly into this vessel and complete its isolation from within the lumen. The liver is then peeled inferiorly using sharp and blunt dissection, and as other hepatic veins are encountered they are isolated and ligated. Between 6 and 8 hepatic veins are found in all. After the last vein is tied, a flimsy vein of gastrohepatic omentum is the only remaining intact structure. This is ligated and the specimen removed.

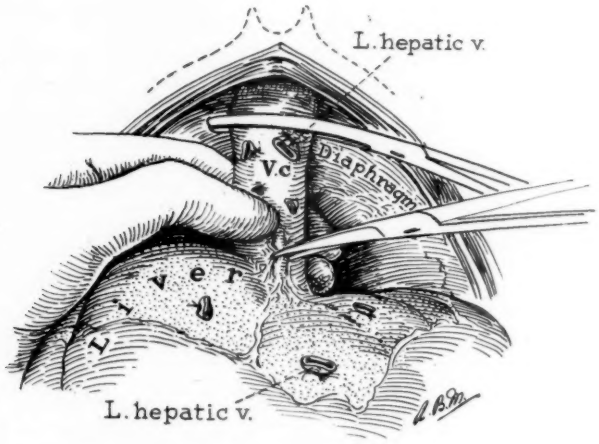

Fig. 2.—After occlusion of the suprahepatic vena cava the liver is removed; hepatic veins are ligated as encountered.

The inferior Pott's clamp is then removed. If any bleeding areas are encountered on the inferior vena cava, these are repaired with arterial silk or ligated. When hemostasis is complete the superior clamp is removed, and portal and inferior caval venous drainage is re-established (Fig. 3).

The operating time, from skin to skin, ranges from 60 to 90 minutes. The measured blood loss is ordinarily between 50 and 200 c.c.

RESULTS

Operative Mortality.—Hepatectomy was attempted on 60 dogs. Two animals died of hemorrhage during the portacaval anastomosis, and a third succumbed 2 hours postoperatively from intra-abdominal bleeding. All other animals were used for study. The survival then in terms of the achievement of

a useful preparation was 95 per cent. It is worth emphasizing that the only dangerous part of the operation is the preliminary portacaval anastomosis. No animal died during the actual removal of the liver.

Postoperative Behavior.—All animals operated upon under ether anesthesia woke promptly and appeared to be entirely normal. At varying times, from 15 to 36 hours, coma developed which was no longer responsive to sugar administration. All dogs studied longer than 24 hours manifested secondary bleeding, either from the incision, or within the abdomen, or both. Until this development the animals urinated frequently and had slow pulses. After the onset of the bleeding tendency, anuria and profound tachycardia occurred and were followed within a few hours by death.

Maximum Survival Time.—The 4 animals studied for maximum survival lived 17, 29, 32, and 42 hours for an average of 30 hours.

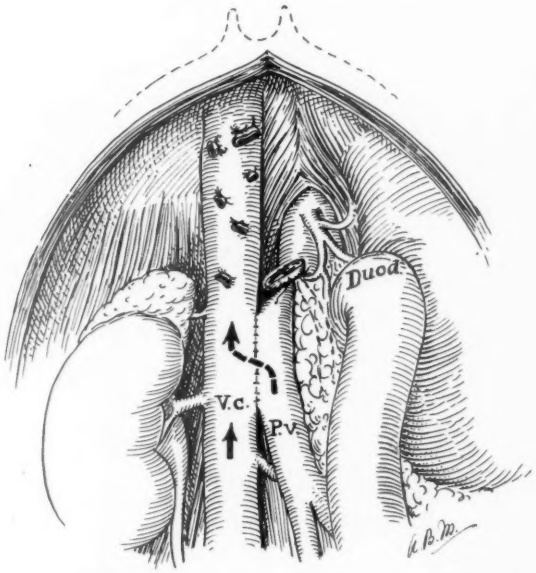

Fig. 3.—Operative field after completion of hepatectomy.

The Effect of the Operation on the Splanchnic and Systemic Circulation.—During the operation there is only one time when the circulatory dynamics of the portal vein and inferior vena cava are not essentially normal. This is during the 15 or 20 minutes while the liver is actually being removed, at which time the inferior vena cava is occluded both above and below the liver. Since at this stage the portal vein has been drained into the vena cava more inferiorly, the portal and venous systems have been converted into a confluent venous pool, and there is concomitant obstruction of the splanchnic venous return.

Experiments were conducted in 3 animals to study the immediate effect of this occlusion on vascular pressures. Shown in Fig. 4 are the changes in the aortic blood pressure and the inferior vena caval pressure in a representative experiment. Since the portacaval systems are in wide communication through

the shunt, the latter may also be considered a portal pressure. In the case shown, a fall in arterial pressure occurred to 80 mm. Hg systolic, coincident with a rise in the portacaval pressure to 350 mm. saline. Once established, the vascular pressures remain relatively stable until the caval clamps are released, following which there is prompt restoration of the pre-existing hemodynamic state (Fig. 4).

Although it was ordinarily necessary to obstruct the portacaval system for only 15 or 20 minutes, it was desirable to know how long this occlusion could be maintained with survival. In 5 dogs obstruction was imposed for one hour. In all animals there was prompt recovery after the clamps were removed.

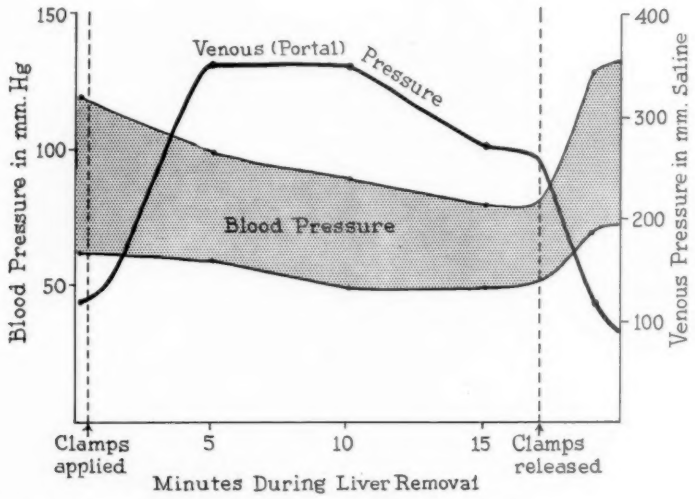

Fig. 4.—Pressures in the arterial and portacaval systems during hepatectomy. See text for explanation.

Autopsy Findings.—Autopsy was performed on most of the animals in this series and on all dogs studied for maximum survival. Thrombosis of the anastomosis, portal vein, or inferior vena cava was not found in any case. In dogs followed less than 20 hours, relatively small amounts of blood-stained fluid were found in the abdomen. Animals followed for longer than this had large amounts of nonclotted blood in the abdomen—sometimes as much as 1,000 c.c. The bowel was grossly normal in all cases, and histologic sections made as late as 42 hours postoperatively were normal (Fig. 5).

DISCUSSION

The described method represents a radical departure from the usual methods of hepatectomy, all of which resect a segment of the inferior vena cava. The only report in which preservation of the inferior vena cava has been described was that of Frank and Jacob.[3] These authors first performed an end-to-side portacaval shunt (necessitating temporary complete occlusion of the portal vein). They then meticulously dissected and ligated the hepatic veins. Because this was not done in a bloodless field, the operation was tedious (3 to 5 hours) and bloody (requiring massive transfusion). Although 3 dogs survived

surgery, the authors recommended that their method not be substituted for the conventional techniques of hepatectomy.

The order in which the technical steps are carried out with the present method deserves further comment. It has been known for a long time that complete occlusion of the portal vein can be done safely in dogs for only a few minutes.[1] Acute occlusion of the inferior vena cava above the renal veins, although eventually fatal, can be tolerated for many hours.[12, 14] The difference in response to acute ligation in the two systems is apparently due to a greater capacity of the occluded inferior vena cava to suddenly utilize collateral channels. With the present method the portal and caval systems are first brought into communication through the anastomosis and when the central drainage of both vascular beds is concommitantly occluded, all collaterals are available to either system. The protective effect of this method was shown in the present study, in which it was shown that combined portacaval obstruction could be tolerated for much longer periods (up to 2 hours) than portal obstruction alone.

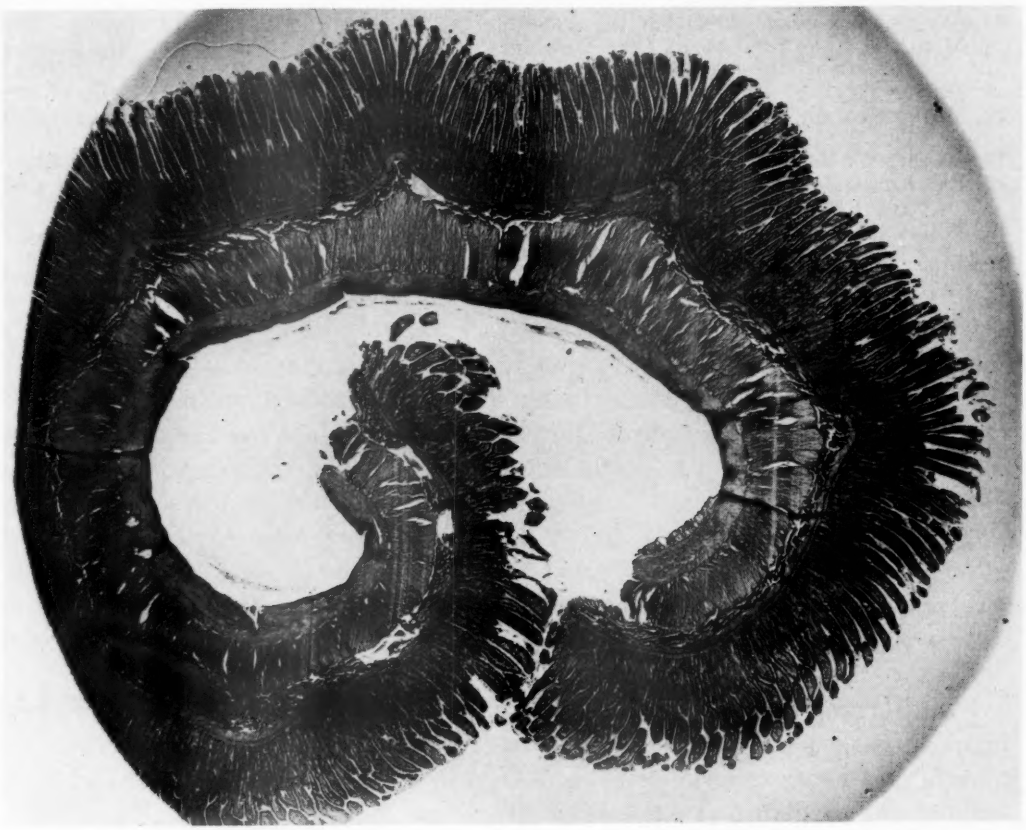

Fig. 5.—Photomicrograph of intestine from dog which survived 42 hours after hepatectomy.

The surgical proficiency necessary to perform this operation is no greater than in other techniques of hepatectomy. The only step that requires unusual care is the formation of the portacaval anastomosis. Because of the elimination of many objectionable features of other methods, this has proved to be for us the most satisfactory method of total hepatectomy.

SUMMARY

A method is described for one-stage complete hepatectomy in dogs with preservation of the inferior vena cava. The method can be done rapidly with minimal blood loss and has a low operative mortality. The maximum survival time compares favorably with other methods of hepatectomy.

REFERENCES

1. Elman, R., and Cole, W. H.: Cause of Death in Acute Portal Obstruction, Tr. Am. Gastro-enterol. A. **36**: 136, 1933.
2. Firor, W. M., and Stinson, E., Jr.: Total Extirpation of Dog Liver in One Stage, Bull. Johns Hopkins Hosp. **44**: 138, 1929.
3. Frank, H. A., and Jacob, S. W.: One Stage Hepatectomy in Dog Preserving Inferior Vena Cava, Am. J. Physiol. **168**: 156, 1952.
4. Freeman, S.: Comparison of Effects of Hepatectomy and of Common Bile Duct Obstruction on Serum Phosphatase of Adult Dogs, Am. J. Physiol. **164**: 792, 1951.
5. Freeman, S.: Studies on Eck Fistulas in Dogs: Simple Technique for Preparation of Portacaval Anastomosis With Aid of Clamp, Surg. Gynec. & Obst. **87**: 735, 1948.
6. Grindley, J. H., and Mann, F. C.: Removal of Liver of Dog: Experimental Surgical Technique, SURGERY **31**: 900, 1952.
7. Leveen, H. H., and Lewis, L.: Simplified One Stage Hepatectomy for Experimental Surgery, Ann. Surg. **139**: 195, 1954.
8. Mann, F. C.: Studies in the Physiology of the Liver. I. Technique and General Effects of Removal, Am. J. M. Sc. **161**: 37, 1921.
9. Markowitz, J.: Experimental Surgery, Baltimore, 1954, Williams & Wilkins Co.
10. Markowitz, J., Lotto, W., Archibald, J., and Downie, H. G.: Hepatectomy; Simple One Stage Method in Dog, A. M. A. Arch. Surg. **64**: 766, 1952.
11. Meyer, W. H., and Starzl, T. E.: The Reverse Eck Fistula, SURGERY **45**: 760, 1959.
12. Polkey, H. J.: The Phenolsulphonphthalein Output After Ligation of the Vena Cava and Renal Veins, Urol. & Cutan. Rev. **33**: 294, 1929.
13. Warren, R., and Rhoads, J. E.: Hepatic Origin of Prothrombin: Observations After Total Hepatectomy in Dog, Am. J. M. Sc. **198**: 193, 1939.
14. Whittenberger, J. T., and Huggins, C.: Ligation of the Inferior Vena Cava, Arch. Surg. **41**: 1334, 1940.

THE RELATIONSHIP OF CARDIAC HYPERTROPHY TO CIRRHOSIS OF THE LIVER

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CIRCULATORY alterations in patients with cirrhosis of the liver suggesting the presence of a venoarterial shunt have been known for some time. Snell[6] in 1935 pointed out that patients with cirrhosis frequently have arterial oxygen saturation well below normal. Kowalski and Abelmann[2] found that in 7 of 22 patients with cirrhosis, the resting cardiac output was elevated and was associated with a large stroke volume and low peripheral resistance. Calabresi and Abelmann[1] and Schoenmacker[5] were able to demonstrate in cirrhotic patients that there were direct communications between the portal venous bed and the pulmonary venous bed.

Further evidence to support the idea that these venoarterial shunts may be functional in about one-third of individuals with cirrhosis has been reported by Lunseth and colleagues,[3] who examined at necropsy the hearts of 108 persons with cirrhosis. They found 12 cases of cardiac hypertrophy, a frequency of 32.4 per cent among the 37 patients with cirrhosis who were found to have neither clinical evidence of hypertension nor pathologic evidence of valvular or arteriosclerotic heart disease.

The results of the examination of our own pathologic material are shown in Figs. 1, 2, 3, and 4. Heart weights were used only from patients in whom there was neither necropsy evidence of heart, renal, or diffuse pulmonary disease of any extent nor clinical evidence of hypertension. A weight of 400 Gm. was considered the upper limit of normal. For women, 22 per cent of the series of 36 patients having heart weights above 400 Gm. had cirrhosis as compared to only 8 per cent in the control group. For the men the evidence is even more striking. Thirty-two per cent of the cirrhosis patients had heart weights over 400 Gm., as compared to the male control series which showed 7 per cent of hearts weighing over 400 Gm.

Since the incidence of cardiac hypertrophy, decreased arterial oxygen saturation, and increased cardiac output, and the anatomic demonstration of venoarterial shunts in the patient with cirrhosis have been reported by different investigators in approximately one-third of the cases examined, the various observations tend to support each other.

In order to determine whether bypass of the portal blood into the arterial system would reproduce the findings in the human with cirrhosis, the following experiment was carried out.

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Fig. 1.

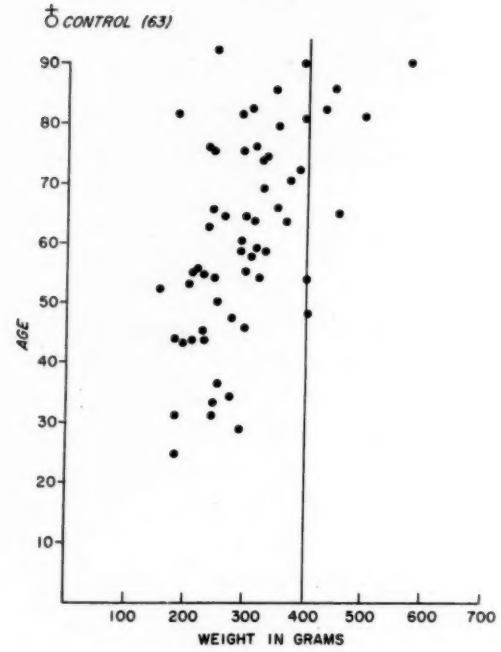
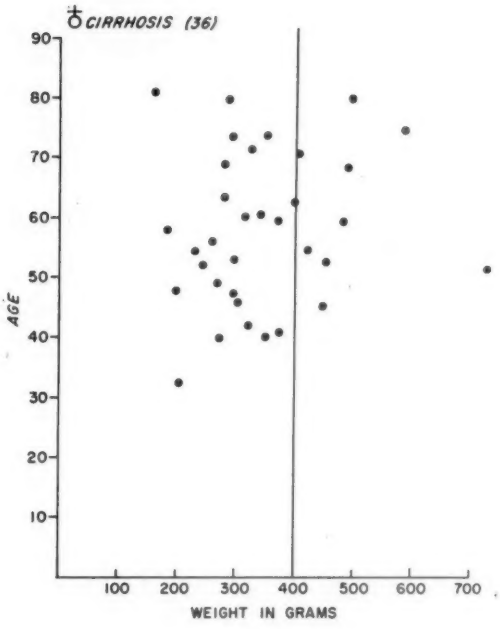
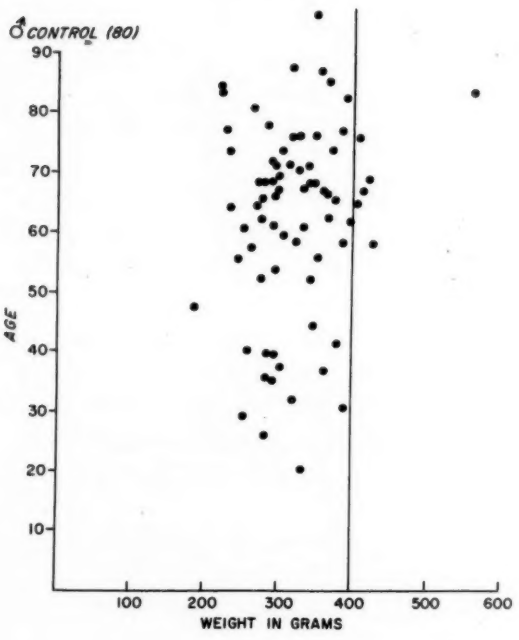


Fig. 2.





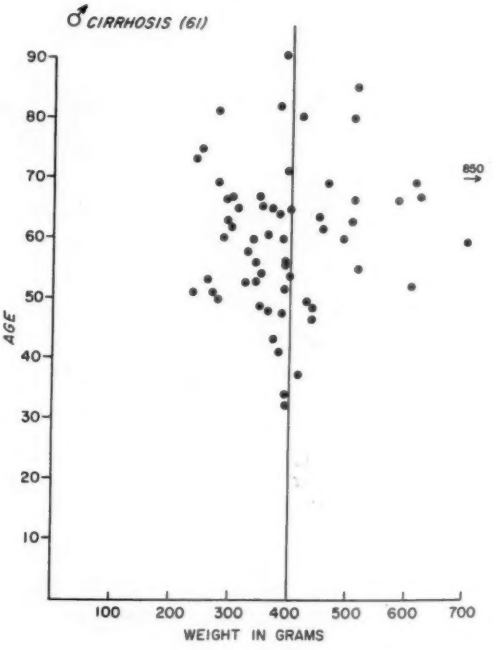


Fig. 3.

Fig. 4.

Fig. 1.—Heart weights plotted against age in female patients without necropsy evidence of primary heart, lung, or kidney disease and without clinical evidence of hypertension.

Fig. 2.—Heart weight plotted against age in females with cirrhosis of the liver and without necropsy primary evidence of heart, lung, or kidney disease.

Fig. 3.—Heart weight plotted against age in males without necropsy evidence of primary heart, lung, or kidney disease or clinical evidence of hypertension.

Fig. 4.—Heart weight plotted against age in males with cirrhosis of the liver and without necropsy primary evidence of heart, lung, or kidney disease.

METHOD

Mongrel stock dogs were anesthetized with Pentothal. An intratracheal tube was then connected to positive pressure and the animal was cooled with ice packs to 32° to 33° C. The right chest was opened widely through the bed of the seventh rib. The aorta is easily approached through this incision in the dog. It was freed up from the arch to diaphragm and all the intercostals were tied. This section was then removed and replaced by a preserved homograft.

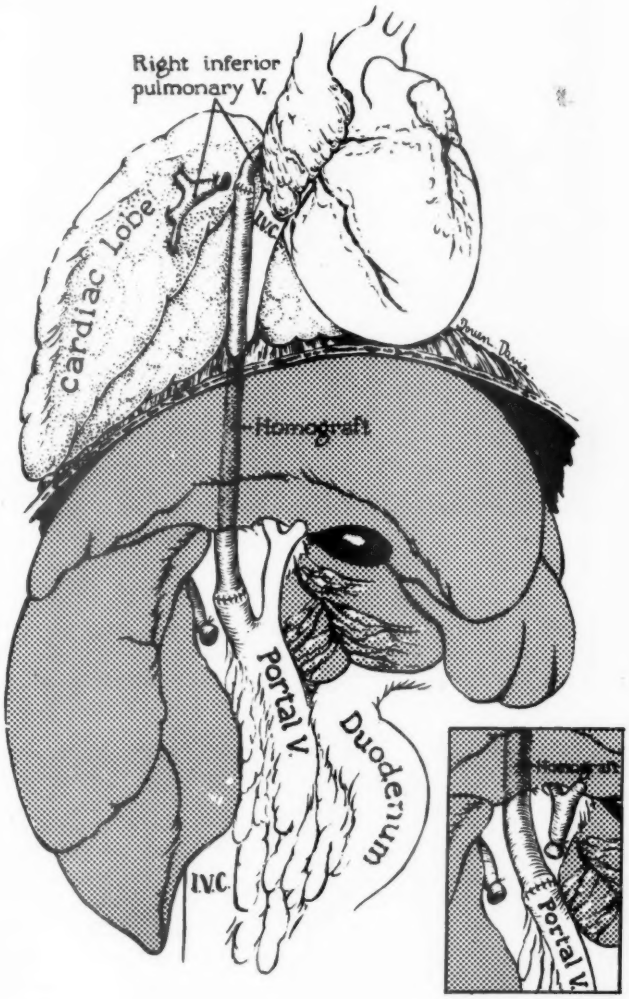


Fig. 5.—Homograft placed between the right branch of the portal vein and joined to the proximal end of the right inferior pulmonary vein. Inset shows same procedure, except that the liver is totally bypassed.

We have found, as have Moore and Riberi,[4] that the animal's own aorta will stay open considerably longer when placed in the venous system than will a preserved homograft.

The right inferior pulmonary vein was freed up to the junction with the left auricle. The distal end was tied. Next the diaphragm was opened and the portal vein was identified to include the bifurcation. The animal's own

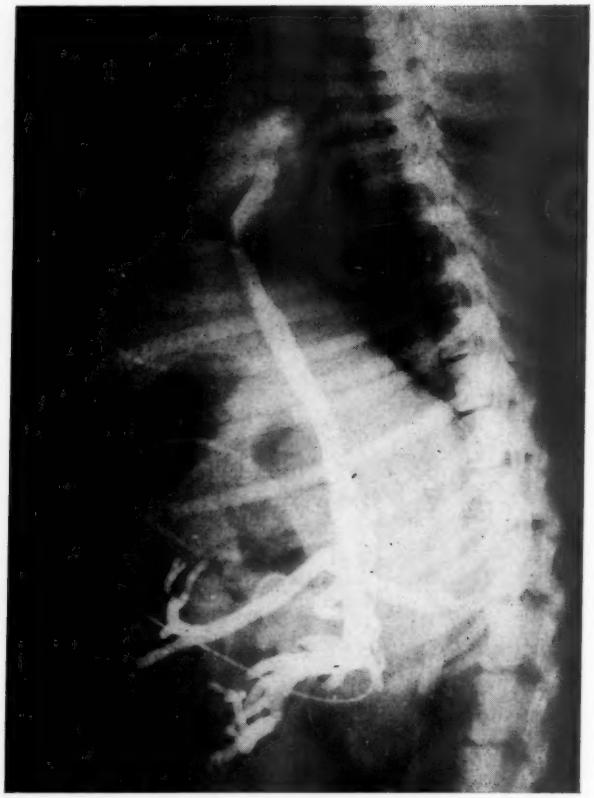


Fig. 6.—Angiogram seventh postoperative day. Dye injected through a polyethylene catheter placed in branch of portal vein. Note filling of left auricle and aorta.

Fig. 7.—Heart of dog C17, 90 days after total liver bypass. Predicted weight 102 Gm., actual weight 162 Gm.

aorta was then placed between the portal vein and the right inferior pulmonary vein as shown in Fig. 5. In 5 animals the right branch of the portal vein was used. The diaphragm was then closed, the chest wall was closed with catheter drainage, and the animal was warmed slowly.

Fig. 6 is an angiogram taken 7 days postoperatively. A polyethylene catheter had been left in a branch of the portal vein. Thirty cubic centimeters of 70 per cent Hypaque injected under pressure shows the graft open with rapid filling of the left heart and aorta.

Fig. 7 shows the heart of an animal examined 3 months after operation. The considerable left ventricular hypertrophy is obvious. Measurement of the cardiac output in this animal (C75) was $\frac{CO}{BV} = 4.0$ c.c. per minute. The normal value in dogs is about 1.2 c.c. per minute, slightly more than a threefold increase in cardiac output.

In Table I, heart weights of animals in which the graft was patent at the end of 100 days are compared to the expected heart weights for the body weight of the animal.

TABLE I. RELATIONSHIP OF HEART WEIGHT TO BODY WEIGHT IN DOGS WITH PORTAL BYPASS

BODY WEIGHT IN KILOGRAMS	PREDICTED HEART WEIGHT IN GRAMS	ACTUAL HEART WEIGHT IN GRAMS
18.2	102	162
17.1	100	147
20.6	119	151
15.2	94	146
7.6	41	60

DISCUSSION

A perusal of autopsy material on patients dying of cirrhosis of the liver will show that about one-third of them will have an "idiopathic cardiac hypertrophy," as compared to normal controls of the same age group. When the various physiologic alterations in cirrhosis which are also reported to occur in about one-third of these persons are considered in conjunction with the anatomic demonstration of venoarterial shunts from the portal bed to the pulmonary venous bed, it seems reasonable to assume that the shunts are responsible for the increased cardiac output and the consequent left ventricular hypertrophy.

It is somewhat disappointing that these shunts are not directly demonstrable clinically. At least none have been pointed out in the large series of splenoportagrams reported from various clinics.

Experimentally total bypass of the portal blood into the left auricle will produce a marked left ventricular hypertrophy. This picture is similar to that seen in the human with cirrhosis.

SUMMARY

1. Evidence is presented to suggest that cardiac hypertrophy occurs in about one-third of humans with cirrhosis.

2. The presence of venoarterial shunts would explain the physiologic and anatomic changes observed.

3. Cardiac hypertrophy can be produced in animals by shunting the portal blood into the left side of the circulation.

REFERENCES

1. Calabresi, P., and Abelmann, W. H.: Portocaval and Portopulmonary Anastomoses in Laennec's Cirrhosis and Heart Failure, J. Clin. Invest. **36**: 1257, 1959.
2. Kowalski, H. J., and Abelmann, W. H.: The Cardiac Output at Rest in Laennec's Cirrhosis, J. Clin. Invest. **32**: 1025, 1953.
3. Lunseth, J. H., Olmstead, E. G., and Abbond, F.: A Study of Heart Disease in 108 Hospitalized Patients Dying of Portal Cirrhosis, A. M. A. Arch. Int. Med. **102**: 405, 1958.
4. Moore, T., and Riberi, A.: Superior Vena Caval Replacement, SURGERY **44**: 898, 1958.
5. Schoenmackers Atlas Postmortaler Angiogramme, Stuttgart, 1954, Georg Thieme Verlag, p. 159, ab. 108.
6. Snell, A. M.: The Effects of Chronic Disease of the Liver on the Composition and Physicochemical Properties of Blood. Changes in Serum Proteins: Reduction in Oxygen Saturation of Arterial Blood, Ann. Int. Med. **9**: 690, 1935.

CHYLOUS PSEUDOANEURYSM

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A previously unreported complication to be added to the long list of possible complications inherent in blood vessel replacement surgery is reported here. This is the development of a "pseudoaneurysm" of an aortic homograft, which at exploration proved to be a chylous cyst surrounding the graft. The symptoms occurred in the early postoperative period and were severe abdominal pain and an enlarging, pulsatile, abdominal mass.

CASE REPORT

A 63-year-old white woman was admitted to the hospital on Nov. 20, 1958, complaining of severe abdominal pain of approximately one week's duration. Approximately one week before entry, she had been in an automobile accident wherein her car was hit from the rear. In the rebound, she struck her abdomen against the steering wheel. Since the accident, she had had increasing abdominal pain. It had been constant, keeping her awake at night, and requiring opiates for control. She had some upper mid-back pain in the lumbar region, but no radiation of the pain into her legs or chest.

Past history revealed that the patient had had a duodenal ulcer in 1957 which had been improved by medical treatment. A year later, a repeat gastrointestinal series showed the ulcer to be healed, but at that time the x-ray suggested the presence of a small aortic aneurysm. This was entirely asymptomatic. The patient had had a hysterectomy, but no serious medical illnesses. She was working as a waitress up to the time of the accident, carrying heavy trays and working long hours.

Physical examination was not remarkable for a woman of this age group, except that there was tenderness along a pulsatile, bulging mass to the left of the midline in the region above the umbilicus. It was especially tender in the left upper lateral border of the mass. The aorta in the upper epigastric region seemed normal in size and the right side of the aorta seemed fairly straight by palpation. The iliac and femoral pulses were easily palpable, and the dorsalis pedis, posterior tibial, and popliteal pulses were bilaterally present and of good quality. There were moderate greater saphenous varicose veins bilaterally. A diagnosis of aortic aneurysm, dissecting or enlarging due to trauma, was made.

On the evening of admission to the hospital, the patient was taken to the operating room. At operation, the abdominal palpatory findings were found to be correct, in that the patient had an aneurysm of the abdominal aorta involving only the straight portion of the abdominal aorta, beginning approximately 2.5 cm. below the renal arteries and ending approximately 0.5 cm. above

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the bifurcation of the aorta. The aneurysm was approximately 5 cm. wide at its widest section. The small bowel and cecum were freed and placed in the Lahey bag outside the abdomen. As the aorta was exposed, it was noted that an unusual number of soft, succulent, lymph nodes were present over the surface of the aorta. The area was quite edematous. There was no free hemorrhage. A straight segment of homologous aortic graft was placed after the aneurysm was removed, and the circulation was re-established to the lower extremities. Good peripheral circulation was demonstrated. The posterior peritoneum was returned to its original anatomic position by replacing the small bowel pedicle in its preoperative site. The posterior peritoneum was not sutured. The anterior peritoneum and fascia were closed with a continuous 1-0 stainless steel suture, approximating the midline incision which extended from the xiphoid process to the pubis. The skin was closed with cotton and bandages placed. The patient left the operating room in good condition.

The patient was placed on continuous nasogastric suction and the immediate postoperative course was very satisfactory. On the first postoperative day her feet were warm and foot pulses were excellent. Her abdomen was soft. On this day, she complained of considerable distress which was thought to be incisional pain. Her intake and output were adequate and her course was considered satisfactory. On the third postoperative day, the patient had good peristalsis present and peripheral pulses were normal; however, she continued to complain of more than the usual postoperative pain. On the fourth postoperative day, the patient's gastric tube was removed and she was started on clear liquids. She tolerated this quite well and on the seventh postoperative day was on a soft diet. She continued to complain of excessive pain localized to the left of the midline. She described this pain as being deep and radiating through to the back. Examination of the abdomen revealed the wound to be healing well. There was tenderness over the graft on deep palpation, which seemed unassociated with the tenderness along the incision. The graft seemed to bow to the left. On the tenth postoperative day, the patient was still having excessive pain requiring opiates for relief. Re-examination of the abdomen revealed the previously described bowing of the graft to be enlarging with a pulsating mass in the left upper quadrant. Because it was suspected that the graft was dilating, or threatening to blow out, an exploratory laparotomy was carried out.

The abdomen was opened through the operative incision, which was healing well. The small bowel was normal in its color, size, and activity. Palpation of the base of the small bowel mesentery revealed an egg-shaped enlargement, suggesting a dilatation of the graft to the size of the preoperative aneurysm. The small bowel was mobilized and removed from the abdominal cavity. The edges of the posterior peritoneum which had been incised at the original operation had healed primarily, with good approximation of the edges. As the base of the mesentery was freed over the graft, a collection of thick, pale yellow fluid was encountered. This had the typical appearance of chyle. The small bowel mesentery was completely freed from the area, unroofing a chylous cyst

which had surrounded the anterior and lateral surfaces of the graft. The graft was undilated and functioning perfectly. The chyle was removed and tedious and careful examination of the area was made for further free flow of the chyle. None could be found. The small bowel was then returned to the abdominal cavity and the posterior peritoneum was replaced in its normal position without suture. The wound was closed as before.

Postoperatively, the patient did very well. She had minimal abdominal tenderness. Her peripheral circulation was normal, and on the third postoperative day she was passing gas. On the fifth postoperative day she was taking a soft diet without difficulty, with practically no abdominal or incisional pain. The wound healed by primary intention and the patient was discharged with a satisfactory result on the eleventh postoperative day.

CONCLUSION

An interesting case of a pseudoaneurysm due to a chylous cyst occurring around an aortic graft is reported. This is the first such reported case.

HEPATIC ARTERY ANEURYSM

Report of a Case Treated by Excision

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THERE have been approximately 125 cases of aneurysm of the hepatic artery reported in the world literature. Only 20, however, have undergone successful surgical treatment. Several excellent reviews[5-7, 9, 11, 12, 15, 18, 20, 25, 26, 28] have correctly emphasized the very dismal prognosis of the untreated lesion. The correct treatment of this condition has been slow in its evolution. Because of this and the limited number of cases recorded, I felt it desirable to describe a case of hepatic artery and abdominal aortic aneurysms treated successfully by excisional therapy.

CASE REPORT

The patient was a 67-year-old white man who was admitted to the hospital on July 9, 1958. He complained of a pulsating mass in his lower abdomen which had been present for approximately 5 years. Both the patient and his referring physician had noticed an increase in its size during the few months immediately prior to his admission. He also stated that he had experienced episodes of epigastric discomfort during the past 5 years which seemed to have no particular relation to meals, but perhaps were aggravated by the ingestion of fatty foods.

He had been treated medically for peptic ulcer 25 years previously. There had been no recurrence of ulcer symptoms. He was, at present, under the care of a urologist because of benign prostatic hypertrophy. The patient denied any cardiovascular disease other than an awareness of an occasional short episode of marked irregularity of his heart rate.

Physical examination revealed a blood pressure of 190/90 and pulsus alternans with a rate of 90 per minute. His heart was not enlarged to percussion, but there was a grade 2 systolic murmur at the apex. There was a mass about 5 by 10 cm. in size located in the middle of the lower abdomen. It was moderately tender to palpation and had intrinsic pulsation. A systolic bruit was heard over it. The other physical findings were essentially normal except for the presence of a small left inguinal hernia and benign prostatic hypertrophy. The peripheral pulses were all present.

The initial laboratory studies revealed a hemoglobin of 13.8 Gm., hematocrit of 42 per cent, and a leukocyte count was 8,000 with a normal differential. The serum cholesterol was 136 mg. per cent, the blood urea nitrogen was 18.5 mg. per cent, a random blood sugar was 111 mg. per cent, and the acid phosphatase was 5.2 units. The urinalysis showed a faint trace of albumin, 4 to 7 leukocytes per high-power field, and 5 to 10 erythrocytes per high-power field.

An electrocardiogram showed a complete left bundle branch block, atrial premature beats from many different foci, and short runs of atrial tachycardia. Roentgenologic findings revealed a normal chest film, calcium in an abdominal aortic aneurysm and calcium in what was interpreted as possibly a splenic artery aneurysm (Fig. 1). An upper

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gastrointestinal series demonstrated a normal esophagus, stomach, and duodenum. A cystlike structure with a fine rim of calcium was seen just to the left of the first lumbar vertebra. This was thought probably to represent a splenic artery aneurysm.

The patient was placed on digitalis and cardiac rhythm difficulties improved. He was operated upon July 21, 1958. At exploration he was found to have an abdominal aortic aneurysm 7 by 8 by 10 cm. in size arising just distal to the renal arteries and ending at the bifurcation of the aorta. He was also found to have an aneurysm of the common hepatic artery which was 4 by 4 by 6 cm. in size (Fig. 2). His gall bladder and other intra-abdominal viscera were normal. The aortic aneurysm was excised and vascular continuity was re-established by the interpolation of a straight, stretch weave Dacron graft between the transected ends of the aorta. The hepatic artery aneurysm was then dissected free. It arose at the origin of the common hepatic artery and ended at the gastroduodenal branch. The hepatic artery was occluded proximally and distally by nonerushing vascular clamps and the gastroduodenal, right gastric, and right and left hepatic arteries maintained pulsatile blood flow. The aneurysm was excised and the transected ends of the hepatic artery were sutured with 5-0 arterial suture.

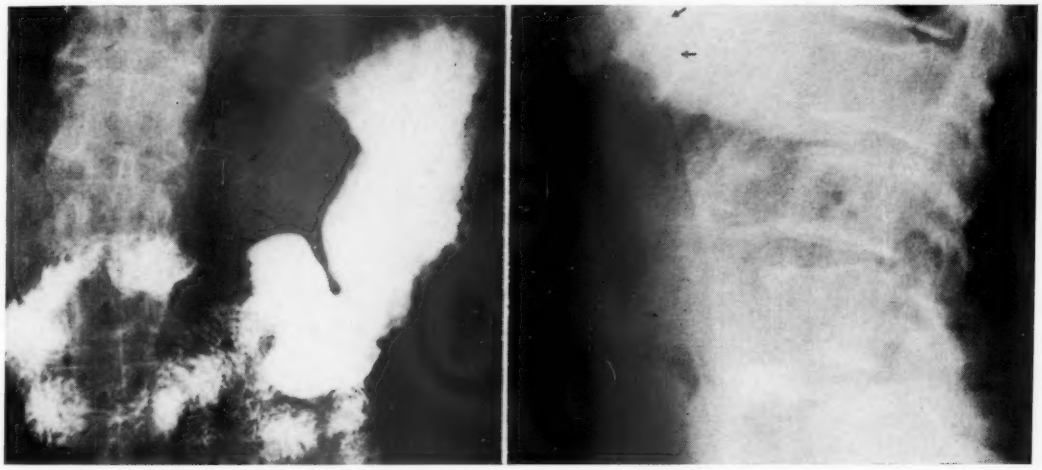

Fig. 1.—Abdominal films demonstrating calcific deposits in the walls of the hepatic and aortic aneurysms.

The patient was placed on antibiotic therapy postoperatively. He made an uneventful recovery and was discharged from the hospital on the fourteenth postoperative day. He remains in good health at present which is now 9 months since his release from the hospital.

Pathologic study of the aneurysms revealed them to be arteriosclerotic in origin.

DISCUSSION

Prior to this report there had been 20 cases of successful surgical repair of hepatic artery aneurysms recorded in the literature (Table I). Mine is the sixth case of total excision of an aneurysm of the hepatic artery. Six have been treated by ligation of the common hepatic artery, 3 by endoaneurysmorrhaphy, 3 by wrapping the aneurysm in cellophane or polythene containing dicetyl phosphate, and one case each by wiring, suture of the liver, and suture of the hepatic artery. This does not include Gordon-Taylor's[8] patient who unfortunately expired 40 hours postoperatively from septicemia and bronchopneumonia. The hepatic artery repair by endoaneurysmorrhaphy was found

TABLE I. SUCCESSFUL SURGICAL CORRECTION OF HEPATIC ARTERY ANEURYSMS

AUTHOR	DATE	AGE	SEX	ETIOLOGY*	LOCATION	HEMORRHAGE	REPAIR
Kehr[17]	1903	29	Male	Infectious	Extrahepatic	Yes	Ligation
Anderson[1]	1919		Male	Arteriosclerotic	Intrahepatic	Yes	Suture of liver
Kading[16]	1919	35	Male	Traumatic	Intrahepatic	Yes	Ligation
Colmers[4]	1921			Traumatic	Intrahepatic	Yes	Ligation
Paul[23]	1951	38	Male	Traumatic	Extrahepatic	Yes	Suture repair of hepatic artery
Dwight[6]	1952	57	Male	Arteriosclerotic	Extrahepatic	Yes	Wiring
Quattlebaum[24]	1954	54	Female	Arteriosclerotic	Extrahepatic	No	Ligation
Guiseffi[10]	1954	52	Female	Arteriosclerotic	Extrahepatic	Yes	Endoaneurysmorrhaphy
Kirklin[18]	1955	52	Female	Arteriosclerotic	Extrahepatic	Yes	Excision
Steelquist[29]	1955	44	Male	Infectious	Extrahepatic	No	Cellophane wrapping
Steelquist[29]	1955	23	Male	Infectious	Extrahepatic	No	Reactive polythene wrapping
Hess[14]	1955	38	Male	Traumatic	Extrahepatic	Yes	Endoaneurysmorrhaphy
Mainetti[19]	1956	57	Female	Traumatic	Extrahepatic	Yes	Ligation
Mainetti[19]	1956	44	Male	Arteriosclerotic	Extrahepatic	Yes	Ligation
Sheridan[26]	1956	27	Male	Traumatic	Extrahepatic	Yes	Endoaneurysmorrhaphy
Inui[15]	1956	33	Male	Traumatic	Extrahepatic	Yes	Excision
Cosco Montaldo[5]	1957	41	Female	Arteriosclerotic	Extrahepatic	No	Excision
Hejnal[12]	1957	38	Female	Traumatic	Extrahepatic	Yes	Excision
Rene[25]	1958	77	Male	Arteriosclerotic	Extrahepatic	No	Cellophane wrapping
Hansbrough[11]	1958	67	Male	Arteriosclerotic	Extrahepatic	No	Excision

*Assumed by author, though often unproved.

to be quite satisfactory at postmortem examination. In addition to these cases Hendrick[13] excised an aneurysm of the gastroduodenal branch of the hepatic artery.

With the collection of more cases the frequency of rupture of hepatic artery aneurysms is becoming even greater than the commonly quoted figure of 80 per cent. It appears that it is only the unusual case that does not ultimately rupture if left alone. That these aneurysms rupture free into the peritoneal cavity, as well as into the biliary tree and gastrointestinal tract, has been emphasized by Barnett and Wagner.[2] Merle, Mabille, and Sotton[22] feel that rupture is so prevalent that perhaps aortography should be done in all cases of gastrointestinal hemorrhage if the etiology of the bleeding is in question.

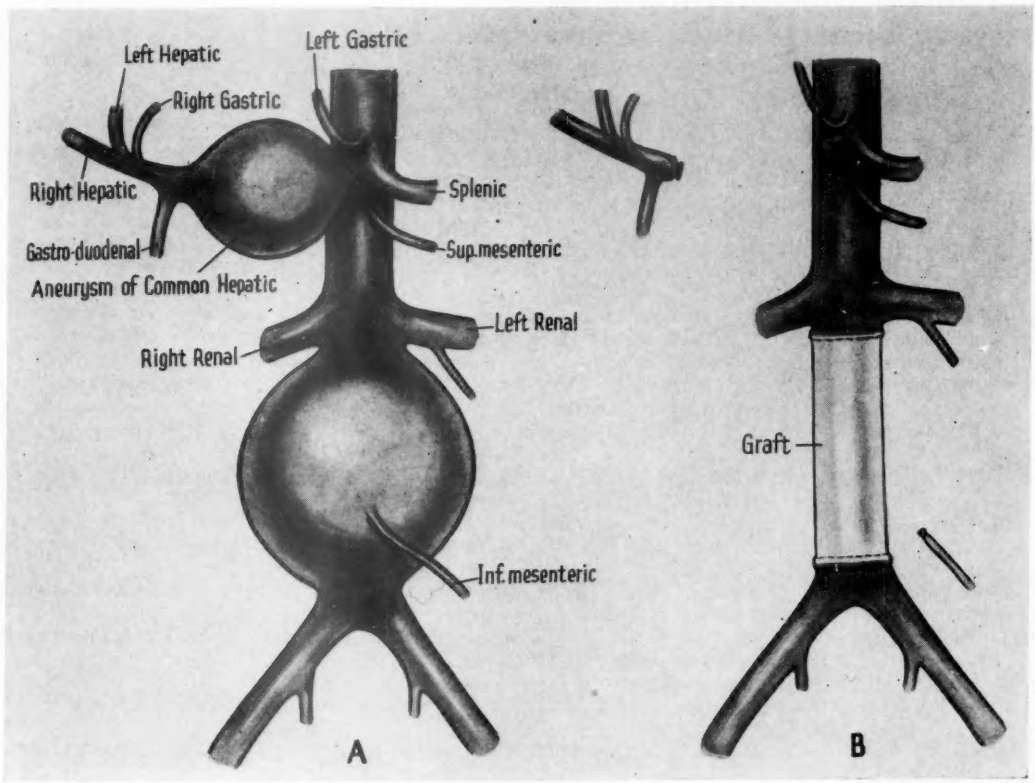

Fig. 2.—Diagrammatic illustration demonstrating the location of the aneurysms and the method of treatment.

Although each of the above-mentioned methods of repair has met with some success, the vast experience, now recorded, with aortic aneurysms would tend to support the belief that, whenever possible, hepatic artery aneurysms should be excised. Bruwer and Hallenbeck[3] have reported a case of a ruptured hepatic artery aneurysm which progressed to fatal hemorrhage even after ligation of the common hepatic artery. The protection from liver necrosis afforded by postoperative antibiotic therapy[21, 30] may offer the surgeon some comfort if he has rendered the liver ischemic; however, the possibility of reconstitution of arterial continuity by direct anastomosis or grafting should not be overlooked.

Shumacker and Siderys[27] have successfully excised a large celiac axis aneurysm and then created an anastomosis between the hepatic artery and the celiac stump. In my case, insertion of a graft was anticipated until the collateral circulation via the gastroduodenal and right gastric branches was found to be adequate.

Hansbrough and Lipin[11] feel that as more cases are reported arteriosclerosis will supersede infection as the most common etiologic agent. This most likely will prove to be true and trauma may well be found to be second in etiologic importance.

SUMMARY

A case of successful excision of hepatic artery and abdominal aortic aneurysm is reported and the pertinent literature reviewed.

REFERENCES

1. Anderson, E. M.: Aneurysm: Report of Cases, Am. J. Surg. **33**: 129, 1919.
2. Barnett, W. O., and Wagner, J. A.: Aneurysm of the Hepatic Artery: A Cause of Obscure Abdominal Hemorrhage, Ann. Surg. **137**: 561, 1953.
3. Bruwer, A. J., and Hallenbeck, G. A.: Aneurysm of the Hepatic Artery: Roentgenologic Features in One Case, Am. J. Roentgenol. **78**: 270, 1957.
4. Colmers, F.: Intrahepatisches Aneurysma und Gallenfistel nach Leberzerreissung. Heilung durch Unterbindung der Arteria Hepatica Communis, Beitr. klin. Chir. **122**: 324, 1921.
5. Cosco Montaldo, H.: Higado desarterializado; primer caso de reseccion en el hombre de la arteria hepatica comun y propia por aneurisma permeable de la arteria hepatica con sobrevida, Bol. Soc. cir. Uruguay **28**: 54, 1957.
6. Dwight, R. W., and Ratcliffe, J. W.: Aneurysm of the Hepatic Artery: Report of a Case Treated by Wiring, SURGERY **31**: 915, 1952.
7. Friedenwald, J., and Tannenbaum, K. H.: Aneurysm of the Hepatic Artery, Am. J. M. Sc. **165**: 11, 1923.
8. Gordon-Taylor, G.: A Rare Cause of Severe Gastrointestinal Hemorrhage With a Note on Aneurysm of the Hepatic Artery, Brit. M. J. **1**: 504, 1943.
9. Grant, J. T., Fitts, W. T., Jr., and Ravdin, I. S.: Aneurysm of the Hepatic Artery: Report of Two Cases and Consideration of Surgical Treatment, Surg. Gynec. & Obst. **91**: 527, 1950.
10. Guiseffi, J., and Collins, C. C.: Successful Care of False Aneurysm of the Hepatic Artery, SURGERY **36**: 125, 1954.
11. Hansbrough, E. T., and Lipin, R. J.: Hepatic Artery Aneurysm With Excision of the Celiac Axis, Ann. Surg. **149**: 273, 1959.
12. Hejnal, J.: Pripad Aneurysmatu Arteriae Hepaticae, Rozhl. Chir. **36**: 420, 1957.
13. Hendrick, J. W.: Treatment of Aneurysm of Pancreatoduodenal Artery by Excision, Ann. Surg. **144**: 1051, 1956.
14. Hess, W., and Celio, A.: Aneurysm of the Hepatic Artery, Helvet. chir. acta **22**: 286, 1955.
15. Inui, F. K., and Ferguson, T. A.: Aneurysm of the Right Hepatic Artery: Preoperative Diagnosis and Successful Excision, Ann. Surg. **144**: 235, 1956.
16. Kading, K.: Ein Geheitter. Fall von Intrahepatischem Aneurysma mit Besonderer Berucksichtigung der Traumatischen Leberarterienanaurysmen, Deutsche Ztschr. Chir., Leipzig **150**: 82, 1919.
17. Kehr, H.: Der Erste Fall von Erfolgrescher Unterbindung der Art. Hepatica Propria wegen Aneurysma, München med. Wchnschr. **50**: 1861, 1903.
18. Kirklin, J. W., Shocket, C., Comfort, M. W., and Huizenga, K. A.: Treatment of Aneurysm of the Hepatic Artery by Excision, Ann. Surg. **142**: 110, 1955.
19. Mainetti, J. M., and Amendolara, J.: Aneurysma de la arteria hepatica, Bol. Soc. cir. Buenos Aires **40**: 173, 1956.
20. Malloy, H. R., and Jason, R. S.: Aneurysm of the Hepatic Artery, Am. J. Surg. **57**: 359, 1942.
21. Markowitz, J., Rappaport, A., and Scott, A. C.: Prevention of Liver Necrosis Following Ligation of the Hepatic Artery, Proc. Soc. Exper. Biol. & Med. **70**: 305, 1949.
22. Merle, H., Mabille, and Sotton: L'anevrysme de l'artere hepatique, Presse méd. **65**: 1161, 1957.

23. Paul, M.: A Large Traumatic Aneurysm of the Hepatic Artery, Brit. J. Surg. **39**: 278, 1951.
24. Quattlebaum, J. K.: Aneurysm of the Hepatic Artery: Report of Three Cases, Ann. Surg. **139**: 743, 1954.
25. Rene, M. L.: Anevrysme de l'artere hepatique decouvert au Decours d'une hemorragie digestive massive, Arch. mal. app. digest., Paris **47**: 561, 1958.
26. Sheridan, J. T.: Hepatic Artery Aneurysm. Report of a Case and Review of the Literature, A. M. A. Arch. Surg. **72**: 300, 1956.
27. Shumacker, H. B., Jr., and Siderys, H.: Excisional Treatment of Aneurysm of the Celiac Artery, Ann. Surg. **148**: 885, 1958.
28. Siew, S.: Aneurysm of the Hepatic Artery: Report of a Case and Review of the Literature, South African J. Clin. Sc. **3**: 143, 1952.
29. Steelquist, J. H.: Aneurysm of the Hepatic Artery: Report of Three Cases, Am. J. Surg. **89**: 1241, 1955.
30. Tanturi, C., Swigart, L. L., and Canepa, J. F.: Prevention of Death From Experimental Ligation of the Liver (Hepatic Proper) Branches of the Hepatic Artery, Surg. Gynec. & Obst. **91**: 680, 1950.

CARCINOID OF AMPULLA OF VATER

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PRIMARY neoplasia of the duodenum is extremely rare. Among the least common tumors found in this area is the carcinoid; only 28 authenticated cases have been reported in the world's literature.[1, 4, 7] Carcinoid involving the ampulla of Vater has been reported only three times.[3, 11, 14] When a disease entity is this rare, individual case reports are justified so that a composite record may be kept and results of treatment evaluated.

This paper will briefly summarize the subject of gastrointestinal carcinoids and describe two new carcinoid tumors involving the ampulla of Vater.

HISTORY

The first recorded case of a carcinoid was described by Lubarsch[9] in 1888 as a tumor of the ileum which was multicentric in origin and lacked gland formation. The term *carcinoid* was coined in 1907 by Oberndorfer[12] because of his impression that they were benign tumors even though the first case with known metastases had already been reported in 1890 by Ransom.

These tumors have also been referred to as argentaffinomas because of the silver-reducing granules which were first noted by Bunting. This term is not entirely accurate since these granules are not always present, particularly in rectal carcinoids. According to Gosset and Masson,[6] carcinoids arise from the Kulchitsky cells of the intestinal epithelium, and they pointed out the similarity of the tumor cells to the chromaffin tissue of paranganglia. This is significant in view of the recently recognized "carcinoid syndrome." A neuroendocrine function for these cells was suggested in 1952 by Biorck, Azen, and Thorson.[2] This was based on work done by Lembeck[8] and others who had extracted serotonin from a "benign carcinoid" tumor and Erspamer,[5] who expressed the belief that serotonin was produced by the chromaffin cells of the intestinal tract. This hypothesis was substantiated by Page and associates[13] who found large amounts of 5-hydroxyindoleacetic acid, a degradation product of serotonin, in the blood and urine of patients with the carcinoid syndrome.

HISTOGENESIS

Kulchitsky or chromaffin cells occur throughout the gastrointestinal tract from the gastric cardia to the anus. The segmental distribution of carcinoid tumors apparently varies in proportion to the number of these cells found in a

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specific area, that is, carcinoids occur most frequently in the appendix and then with decreasing frequency in the terminal ileum, jejunum, rectum, colon, cecum, stomach, gall bladder, and duodenum.

DISCUSSION

McDonald,[10] in reporting the largest single series of carcinoids of the gastrointestinal tract, stated that, of 356 tumors, only 207 (58 per cent) were appendiceal in origin, which differs from the usual figures of 90 per cent plus found in the literature. Appendiceal carcinoids are notably less malignant than extra-appendiceal carcinoids; no case of spread beyond regional nodes has been reported in the English literature. Pathologists generally agree that malignancy of carcinoids cannot be determined by cytology alone because the usual criteria of cell anaplasia and mitosis are not applicable to these tumors. Malignancy must then be determined by the demonstration of metastasis or microscopic invasion. McDonald found that, in all but one of the cases in his series in which carcinoid had spread to lymph nodes or other organs, the primary tumor had involved underlying muscle coats and lymphatics. He also found that, in all cases in which metastasis had occurred in the liver and distant organs, regional lymph nodes adjacent to the primary tumor were involved. Consequently, he postulated that malignant carcinoid follows a progressive pattern of invasion, first involving muscle coats, then spreading by lymphatics to regional nodes, and passing to the liver by blood vessel invasion. Using these criteria, he evaluated invasiveness in 146 extra-appendiceal carcinoids as follows: 33 per cent were not invasive, 27.3 per cent involved muscle coats only, 23.3 per cent spread to regional nodes, and 16.4 per cent had spread to distant organs.

CASE REPORTS

CASE 1.—E. J., a 57-year-old Negro farmer, was admitted to the Jackson Veterans Administration Hospital on July 29, 1953, with a history of intermittent jaundice and generalized pruritus for 2 years without gastrointestinal symptoms or weight loss. Stools varied from white to yellow in color with dark foamy urine. There had been no history of palpitation, tachycardia, asthma, or flushing episodes. On examination the sclera were slightly icteric. The heart and lungs were normal. The liver was palpable five fingerbreadths below the costal margin and was smooth and nontender.

X-ray of the chest revealed no abnormalities of the heart and lungs; however, there was slight tortuosity and uncoiling of the aorta. Laboratory studies were as follows: Hemoglobin 15 Gm., white blood cell count 6,000 with a normal differential, normal urinalysis, total protein 6.0 Gm. per cent and albumin-globulin ratio 4.2/1.8, icterus index 22, serum bilirubin 4.3 mg. per cent, direct 2.9, indirect 1.4, serum cholesterol 752 with 73 per cent cholesterol esters, alkaline phosphatase 41, cephalin flocculation negative, thymol turbidity 3.3, and prothrombin time 12.5 seconds as compared to a control of 12.2 seconds. Repeat liver profile 8 days later revealed serum bilirubin to be 12.8 with 5.1 direct and 6.7 indirect, alkaline phosphatase 55 mg. per cent, cephalin flocculation 1+, and thymol turbidity 3.3; serology was negative, and an ECG was within normal limits.

The patient was operated upon on Aug. 27, 1953, through a right subcostal incision. The gall bladder was markedly enlarged and contained 600 c.c. of bile. The common duct was dilated to 3 cm. in diameter. A choledochostomy was performed and a mass was palpated in the region of the ampulla of Vater. The duodenum was then opened anteriorly and a

1.5 cm. mass was visualized at the ampulla. Several lymph nodes found adjacent to the second portion of the duodenum were removed for histologic examination. There were no palpable metastases in the liver. The tumor was resected by dividing the duodenal mucosa widely around the base and extending through the wall of the duodenum in this area. The common duct was transected 2 cm. proximal to the neoplasm. The duct of Wirsung was also transected. These two ducts were then reapproximated to the duodenum in two layers using interrupted 3-0 chromic catgut sutures. A long arm Cattel T-tube was inserted into the common duct and brought through the choledochoduodenal anastomosis into the duodenum.

Postoperatively the patient did well until the third day, when he had a sudden episode of shock and the serum potassium was found to be 1.34 mEq. per liter. This was successfully treated with parenteral potassium, and he continued to improve and was discharged on Sept. 9, 1953, with the T-tube in place.

Permanent pathologic sections were reported as carcinoid of the ampulla of Vater with metastasis to one lymph node.

Since discharge on Sept. 9, 1953, the patient has been entirely asymptomatic. On Nov. 16, 1954, the T-tube was removed. Periodic checkups to date reveal normal upper gastrointestinal x-ray studies except for some irregularity at the site of duodenotomy. A determination of the 24-hour urine serotonin excretion is within normal limits at this time, which is 5½ years following operation and 7½ years since onset of symptoms.

CASE 2.—J. D., a 69-year-old Negro farmer, was admitted to the Jackson Veterans Administration Hospital on Jan. 16, 1958, with a 2-year history of intermittent abdominal pain. Pain was cramping in character and radiated to both scapular areas. Attacks usually began with a chill followed by fever and were accompanied by light-colored stools and dark urine. He also noticed that he was jaundiced with these episodes. He had lost approximately 16 pounds during the preceding year. There had been no history of palpitation, tachycardia, asthma, or flushing episodes. Examination revealed the heart and lungs to be normal. The sclerae were icteric. The abdomen was soft and protuberant with a smooth nontender liver palpable two fingerbreadths below the costal margin.

Laboratory examinations revealed urinalysis normal, complete blood count normal, stools for occult blood negative, a trace of urine bilirubin, alkaline phosphatase 13.5, total protein 7.6 Gm. per cent with an albumin-globulin ratio of 4.8/2.8, serum bilirubin 3.5, thymol turbidity of 1.0, and cephalin flocculation negative. ECG was within normal limits and chest x-ray was normal except for old Ghon complex. Visualization was not obtained by a cholecystogram. An upper gastrointestinal series showed an area in the distal portion of the descending duodenum where there was delay in passage of the barium and a fairly well-circumscribed filling defect with definite distortion of the mucosal pattern (Fig. 1).

He was operated upon on Jan. 27, 1958, through a right upper paramedian incision. A firm mass was palpated in the duodenum at the ampulla of Vater. The duodenum was opened anteriorly and a tumor mass measuring 3.5 cm. in diameter was found involving and completely occluding the ampulla (Fig. 2). The mucosa over the neoplasm was intact. A frozen section of the tumor was reported as carcinoid. There was no evidence of metastasis in the liver. Several regional lymph nodes removed and biopsied were reported as negative for tumor. The entire lesion with the distal third of the common duct was widely resected.

TABLE I. CASE 2. SEROTONIN VALUES
(5-Hydroxyindole-3-Acetic Acid in 24-Hour Urine Expressed in Milligrams)

Normal	3.0 to 8.0
First postoperative day	11.5
End of first week	7.8
End of second week	7.4
End of fourth week	5.8
End of fifth month	4.6
End of twelfth month	4.8

Serotonin determination on the first postoperative day was elevated, which we assume was due to manipulation of the tumor. Subsequent studies have been within normal limits.

Fig. 1.

Fig. 2.

Fig. 1.—Case 2. Anteroposterior projection of upper gastrointestinal series showing a well-outlined filling defect in the descending duodenum at site of ampullary carcinoid.

Fig. 2.—Case 2. The duodenum has been opened anteriorly, revealing a 3.5 cm. carcinoid involving the ampulla of Vater.

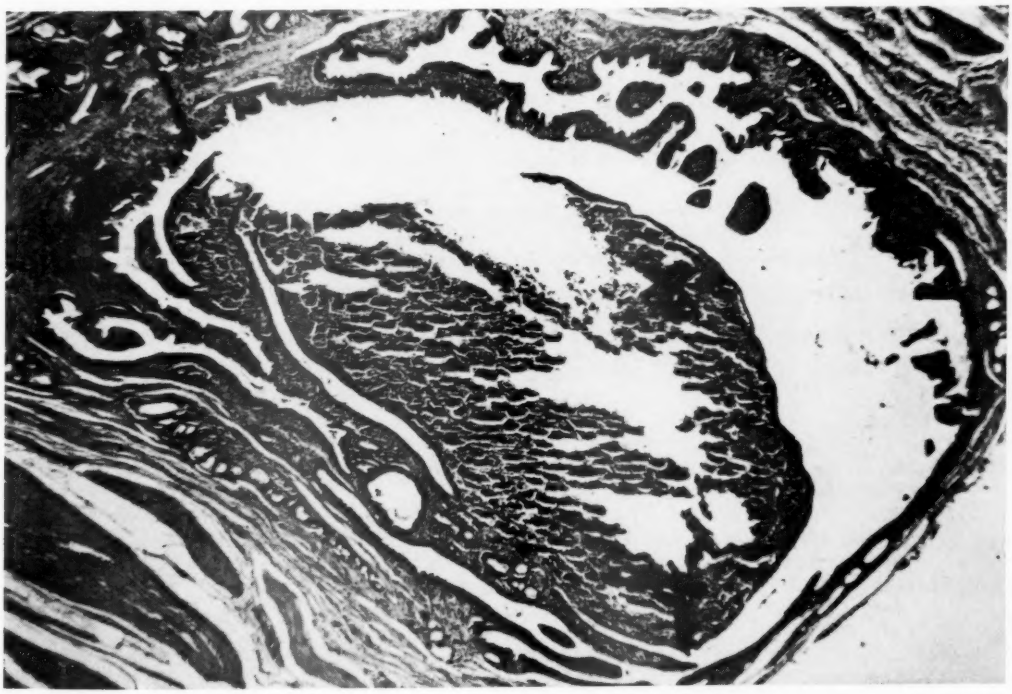

Fig. 3.—Case 2. Photomicrograph (×20) showing carcinoid within the ampullary portion of the common duct.

The common duct was reapproximated to the duodenum in two layers using interrupted 3-0 chromic catgut sutures. A T-tube was inserted in the dilated common duct and brought through the choledochoduodenal anastomosis into the duodenal lumen.

The patient had an uneventful postoperative course. The serum bilirubin and alkaline phosphatase gradually returned to normal levels over a period of 6 weeks. The patient has remained asymptomatic and without evidence of recurrence to date, which is one year following surgery and 3 years since onset of symptoms. Serotonin studies have remained within normal limits (Table I).

METHOD OF MANAGEMENT

Both of the preceding cases were treated by wide local excision of the tumor mass with reimplantation of the common duct into the duodenum. This is considered preferable to radical pancreatoduodenectomy. Of all duodenal carcinoids reported, only 15.8 per cent metastasized beyond regional nodes, which is less than the usual operative mortality (20 to 30 per cent) for pancreatoduodenectomy. Resection should be performed even in the presence of obvious liver metastasis because of the known tendency for carcinoids to produce duodenal obstruction and because of the generally good life expectancy in these slowly growing tumors. Extra-appendiceal carcinoids should be considered low grade malignant neoplasms which usually spread slowly and progressively. Without lymph-node involvement wide local resection is probably adequate for noninvasive carcinoids and those involving only the muscle coats of the bowel wall. If regional lymph nodes are involved, local resection combined with removal of nodes is indicated. Even in the presence of liver and other distant metastasis, resection of the tumor mass with its metastatic spread is advised because of the usual slow rate of progression of these neoplasms. This is especially important in patients with the carcinoid syndome as they may obtain great relief of symptoms particularly if the cardiac lesions are not advanced.

SUMMARY

A brief review of carcinoids of the gastrointestinal tract has been presented with particular emphasis on a logical plan of management.

Two new cases of carcinoid involving the ampulla of Vater have been reported, which brings the total number of cases in the literature to five.

REFERENCES

1. Barnes, Z. B., and Young, J. M.: Carcinoid Tumors of the Duodenum, SURGERY 40: 992-929, 1956.
2. Biorck, G., Azen, O., and Thorson, A.: Unusual Cyanosis in a Boy With Congenital Pulmonary Stenosis and Tricuspid Insufficiency. Fatal Outcome After Angiocardiography, Am. Heart J. 44: 143, 1952.
3. Brunschwing, A., and Childs, A.: Resection of Carcinoma (Carcinoid) of the Infrapapillary Portion of the Duodenum Invading the Ampulla of Vater, Am. J. Surg. 45: 320, 1939.
4. Ebert, R. E., Parkhurst, G. F., Melendy, O. A., and Osborne, M. P.: Primary Tumors of the Duodenum, Surg. Gynec. & Obst. 97: 135, 1953.
5. Erspamer, V.: Il sistema cellulare enterochromaffine e l'enteramina, Rendiconti Scientifici Famitalia, Vol. I, 1954.
6. Gosset, A., and Masson, P.: Tumeurs endocrines de pappendice, Presse méd. 22: 25, 1914.
7. Horsley, J. S., and Golden, B. N.: Carcinoid Tumors of the Duodenum, Surg. Gynec. & Obst. 105: 417, 1957.

8. Lembeck, F.: 5-Hydroxytryptamine in a Carcinoid Tumor, Nature **172:** 910, 1953.
9. Lubarsch, O.: Über den primaren Krebs des Ileum nebst Bemerkungen über das gleichzeitiger Vorkommen von Krebs und Tuberkulose, Virchows Arch. path. Anat. **111:** 280, 1888.
10. McDonald, R. A.: A Study of 356 Carcinoids of the Gastrointestinal Tract, Am. J. Med. **21:** 867-878, 1956.
11. Mrazek, R. G., Jr., Godwin, M. C., and Mohardt, John: Carcinoid Tumors; a Clinical and Pathologic Study of 27 Cases, Surg. Gynec. & Obst. **96:** 661, 1953.
12. Oberndorfer, S.: Karzenoide Tumoren des Dunndarms, Frankfurt. Ztschr. Path. **1:** 426, 1907.
13. Page, I. H., Corcoran, A. C., Undenfriend, S., Sjoerdsma, A., and Weissbach, H.: Argentaffinoma as Endocrine Tumor (letters to the editor), Lancet **1:** 198, 1955.
14. Warren, K. W., and Coyle, E. B.: Carcinoid Tumors of the Gastrointestinal Tract, Am. J. Surg. **82:** 372, 1951.

CATGUT, SILK, AND SILVER—THE STORY OF SURGICAL SUTURES

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THE search for the perfect surgical suture material has been a long and laborious one and is not yet ended. The ideal material would be a perfect union of easy sterilization, adequate tensile strength, handling ease, absence of foreign body reaction, and complete tissue absorption. Such a suture has yet to be developed. Much has been accomplished, nonetheless, and the sutures so much taken for granted in modern surgery are the result of trials and disappointments of a long succession of physicians.

The origin of surgical suture material is obscure although a reference can be found in ancient Egyptian literature. The Edwin Smith Papyrus, written some 4,000 years ago, mentions wound edge approximation with linen adhesive plaster and sutures most likely of the same material. The Caraka Samhitá (1,000 B.C.) of India details the use of ants as suture material. The practitioner took ants with large heads, brought together the wound edges and applied the ant with gaping mouth to the incision. As soon as the mouth was closed, the head was cut off leaving the jaws permanently closed. A row of such ants was applied to effect wound closure especially in intestinal surgery. This practice continued for many centuries in Africa and even in recent years in South America.

The Indian surgeon Súsruta,[20] around 600 B.C., completed his *Compendium of General Medicine* in which are described many materials for suturing—plaited horsehair, cotton, strips of leather, fibers from the bark of the Ashmántaka tree, and animal sinews. In Rome, Celsus during the first century A.D. employed long threads of unknown material which were used to ligate blood vessels, the first such description. The sutures protruded from the wound so that their removal would be easy. Galen[5] refers to catgut in his *De methodo medendi* (circa A.D. 175):

> Choose from those materials where you are living that material which is least putrescible such as very thin catgut which rots easily and quickly falls from the vessel.

According to Ziegler[24] the word *catgut,* used for centuries to describe suture material made from twisted sheep intestines, is derived from the term *kitgut* or *kitstring*—the string or cord use on a *kit* or *fiddle.* Confusion arose with kit, meaning young cat; hence, in the grown animal, *cat* or *catgut.*

Following Galen came many physicians who recorded their use of suture material—Antyllus (circa A.D 200) who used catgut and Celtic linen; Paul of Aegina (A.D. 625-690) who used woolen threads as well as horse and human hair; Rhazes of Bagdad (A.D. 860-932) who used harpstrings. Trotula (circa A.D.

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1050), a female obstetrician of Salerno, described the use of silk sutures in perineorrhaphy in her treatise, *Concerning the Cure of the Diseases of Woman, Before, During, and After Delivery.*

The first to recognize the importance of isolated rather than en masse ligature of tissue was the fifteenth-century surgeon, Leonardo Bertapaglia of Padua. He utilized a linen thread with which he took a stitch in the blood vessel wall after tying the suture. Ambroise Paré (1517-1590), following the earlier example of Giovanni deVigo of Genoa and Alphoneus Ferrus, repopularized the use of the ligature after a period of extensive experimentation. Although he did not originate the ligature, he is given credit for emphasizing it as being better than cautery which had become well established in the preceding century as the best way to control hemorrhage. Wire sutures fashioned of gold were introduced by Hieronymus Fabricius Ab Aquapendente (1537-1619) at Padua. The flexibility and lack of tissue-cutting properties appealed to him. He also used linen thread impregnated with gum of tragacanth in his operations.

One of the great problems during centuries past was infection which accompanied all sutured wounds. Very little elective surgery was possible because of the inevitable sepsis. Nonabsorbable materials were almost always utilized and catgut was neglected. At the turn of the nineteenth century, Dr. P. S. Physick of Philadelphia observed the action of wound discharges in dissolving buckskin ligatures which were placed in wounds in horses. Many different absorbable materials were tried experimentally—parchment, tendon, fish intestine, varnished leather, and finally catgut. Luigi Porta, Professor of Surgery in Pavia, in 1840 demonstrated catgut to be the most homogeneous and strongest substance for a suture material and its use became widespread. Unfortunately infection remained a primary problem. In 1869 Joseph Lister[13] in a continuation of his work on sepsis introduced suture sterilization:

> And I conceived that if a silk thread, steeped in some liquid capable of destroying the septic organisms in its interstices, were tied round an artery, and left with short-cut ends in a wound dressed antiseptically, the foreign body, soon losing by diffusion into the circulation, the stimulating salt with which it was saturated at the outset, and being in its own substance as unstimulating as a pellet of lead from a fowling-piece, would either remain, like the latter, permanently encapsulated or itself experience absorption together with the dead tissue in its grasp.

He also experimented with catgut sterilization:

> The method which I have found to answer best is to keep the gut steeping in a solution of carbolic acid in five parts of olive oil, with a very small quantity of water diffused through it.

Lister later discovered that chromic acid impregnation of catgut delayed its absorption, a method still employed by manufacturers today.

Not all physicians agreed that suturing of wounds was a necessity for healing. In a series of lectures to medical students delivered in 1807 Samuel Young[23] of the London College of Surgeons vigorously denied the need for sutures at all:

> And I defy any one to prove the necessity of sewing a Wound ... nor is there a Surgeon breathing who has been in the constant habit of sewing Wounds, that can give any other reason for his practice than that such has been the custom .... the Principles of Adhesion [healing] had been grossly abused, perverted and destroyed, by the cruel practice of stitching Wounds, yet I concluded such were only barbarous relics of those Rules of Surgery. And although the use of the Thread Suture professes, and does bring the sides of a wound together, yet in effect, so far as the nature of Adhesion is concerned, it is no other than placing a piece of lint between two wounded surfaces. A Surgeon courts adhesion by the Thread Suture, as a specious knave advises his friend to adopt measures for his good, which a thousand to one will end in his ruin.

Young was a proponent of the adhesive plaster for wound closure. He detailed the disadvantages of suture material and the advantages of adhesive plaster in his bitter, but amusing, dissertations. He summed up by stating:

> ... the adhesive strap ... *has none of the disadvantages* of the thread suture ... can never act as a foreign body ... can no more produce a "partial stricture," than the use of the thread suture can avoid it.

J. Marion Sims[19] experimented with silver wire as a suture material because of dissatisfaction with silk and catgut in his early repairs of vesicovaginal fistulas. It worked well and became the standard for use in all of his operations whether for amputation, mastectomy or fistula repair. On Nov. 18, 1857, in the Anniversary Discourse to the New York Academy of Medicine he described his discovery and its first use in a vesicovaginal fistula operation:

> ... I happened to pick up a piece of brass wire, that had been used in a pair of old-fashioned suspenders made before the days of India rubber; it was as fine as ordinary sewing thread. I took it to a jeweller, who imitated it in silver. ... A young colored woman ... was placed on the operating table for the thirtieth time, and the silver wires were applied. ... In all previous operations the urethra, in a day or two, would become red and tender, and the urine loaded with thick tenacious mucus, thus showing the inflammatory process, which was adverse to union; but after this operation, the urine remained perfectly limpid all the time, and on the eighth day the parts were perfectly healed.

Clinton Cushing,[4] writing in 1889, took exception to the need for silver wire and successfully used readily available violin strings in his gynecologic operations. The material was sterilized by his own painstaking method. His description resembles a muscial score:

> I purchased from the wholesale dealers in musical instruments several boxes of the three sizes of catgut string used on the violin. The largest size, or D string of the violin, I used for ligating the pedicle in ovariotomy, and for repairing the perineum. The A string, or middle size, I used for repairing the cervix, and for buried sutures either in the perineum or in the abdominal wall. The E string, or smallest size, I used for ligating adhesions and bleeding vessels in the abdominal cavity.

During the same period Theodor Kocher[11, 12] became impatient with catgut sutures because of the great many wound infections which occurred and he began to advocate silk. With the latter material the incidence of wound infections in his clinic became significantly less. William Halsted visited Kocher in the 1880's and was impressed with the latter's experience with silk. He

returned to America and in 1882 began to use silk routinely in his operations. Nine years later Halsted[9] published the first of a series of reports on his surgical technique and instrumentation:

> I believe that the obstruction to the circulation produced by sutures and ligatures is often the immediate cause of suppuration in infected wounds.... The complete strangulation of large masses of tissue we try to avoid by using very weak silk for the sutures and ligatures. The occasional breaking of the silk reminds one that he is tying with too much force or that he has included too much tissue in his ligature. Inasmuch as we cannot disinfect the skin thoroughly we never perforate the skin with a suture. The skin wound is invariably closed by "buried skin sutures". These sutures are taken from the undersurface of the skin.

This was the beginning of a surgical era which promulgated careful technique and the use of silk sutures.

In 1913 Halsted[8] published a further exposition of his surgical ideas. He had become convinced by that time that silk sutures were superior to any other material and offered his opinions:

> The relatively high cost of catgut, its bulkiness, the inconveniences attending its use in sterilization, its inadequacy, the uncertainty as to the time required for its absorption, and the reaction it excites in a wound, induced me to discard it completely for clean wounds in the surgery both of the human subject and of animals. From year to year and for various periods of time I have given the catgut, sterilized by the best known American purveyors of this material, a trial but invariably with the results which we interpreted as being less perfect than with silk.... With this fine silk in the wounds, which for 23 years have, as a rule, been closed without drainage, suppuration almost never occurs.

During the years following Halsted's publication a great controversy raged among American surgeons as to whether silk or catgut was superior. Halsted-trained surgeons were the only ones who used silk exclusively. It was only after some 20 years following Halsted's definitive article in 1913 that Allen Whipple,[22] one of the foremost American surgeons, passed approvingly on silk technique as being outstandingly better than catgut and it became generally accepted.

Sepsis in catgut-sutured wounds, however, remained a problem. Despite the best efforts of the catgut manufacturers, sterility could not be assured for all of the catgut produced. Pyogenic organisms were eliminated adequately by sterilization techniques whether by heat or chemicals. The spore-forming organisms, however, persisted and infection with such organisms was common in wounds. In 1929 in England Bulloch[2] investigated this problem and made recommendations concerning procedures to render catgut sterile. The British Government shortly thereafter made it illegal to produce catgut by methods other than those which could assure the surgeon a sterile product.

Five years later in the United States Meleney and Chatfield[15] found a large number of specimens of catgut from reputable manufacturers to be contaminated with spore-forming bacteria. They devised a method for testing catgut sterility which, with some modifications by Clock,[3] is still in use today. Preparation standards were made a legal requirement by the United States Pharmacopoeia[21] in 1940. Today heat methods are used for suture sterilization and in addition irradiation methods with electron beams have become prominent.

Other materials have been proposed for suture use in recent decades—steel wire, umbilical cord, canine nerves, kangaroo tendon, cotton, fascia, and synthetic plastics. Babcock,[1] who introduced alloy steel wire, felt that "for surgical purposes it may be substituted for the weaker and more brittle silver and bronze wires and replace, with advantage, horsehair, silk and 'dermal' as a fine approximating suture." Meade and Ochsner[14] reawakened interest in cotton especially because of its ease in handling and in sterilization. More recently synthetic plastic materials have been introduced with excellent results. Tissue toleration is maximal and tensile strength is excellent.

Samuel C. Harvey,[10] who did so much of the pioneer investigative research into wound healing summed up the suture problem in an editorial in 1934:

> The absorbable suture, while not rendering refinement of technique any the less desirable, permits rougher handling of tissues, a certain degree of infection and a grosser but more rapid technique, without in most instances materially increasing the disability of the patient. On the other hand, the nonabsorbable suture enforces meticulousness on the part of the surgeon so that he becomes more of the artist, though none the less a craftsman.

REFERENCES

1. Babcock, W. W.: Ligatures and Sutures of Alloy Steel Wire, J. A. M. A. **102**: 1756, 1934.
2. Bulloch, W., Lampitt, L. H., and Bushill, J. H.: The Preparation of Catgut for Surgical Use, Medical Research Council, Special Report No. 138, London, 1929, His Majesty's Stationery Office.
3. Clock, R. O.: A Reliable Method for Testing the Sterility of Surgical Catgut Sutures, Surg. Gynec. & Obst. **61**: 789-793, 1935.
4. Cushing, C.: Ligatures and Sutures, What Material Shall Be Used? Tr. Am. A. Obst. & Gynec. **2**: 168-176, 1889.
5. Galen: De methodo medendi, Book 13.
6. Gallie, W. E., and LeMesurier, A. B.: The Use of Living Sutures in Operative Surgery, Canad. M. A. J. **11**: 504-513, 1921.
7. Gudger, E. W.: Stitching Wounds With the Mandibles of Ants and Beetles, J. A. M. A. **84**: 1861-1864, 1925.
8. Halsted, W.: Ligature and Suture Material: The Employment of Fine Silk in Preference of Catgut, J. A. M. A. **60**: 1119-1126, 1913.
9. Halsted, W.: The Treatment of Wounds With Especial Reference to the Value of Blood Clot, Johns Hopkins Hosp. Rep. **2**: 305-306, 1891.
10. Harvey, S. C.: Concerning the Suture, Surg. Gynec. & Obst. **58**: 791-792, 1934.
11. Kocher, T.: Eine einfache Methode zur Erzeilung Sicherer Asepsis, Corresp. Blat. Schweiz. Aerzte. **18**: 3, 1888.
12. Kocher, T.: Zubereitung von Antiseptischen Katgut, Zentralbl. Chir. **8**: 353-358, 1881.
13. Lister, J.: Observations on Ligature of Arteries on the Antiseptic System, Lancet **1**: 451-455, 1869.
14. Meade, W. H., and Ochsner, A.: Spool Cotton as a Suture Material, J. A. M. A. **113**: 2230-2231, 1939.
15. Meleney, F. L., and Chatfield, M.: The Sterility of Catgut in Relation to Hospital Infections, Surg. Gynec. & Obst. **52**: 430-441, 1931.
16. Melle, G. J.: Early History of the Ligature, S. African M. J. **8**: 290-292, 1934.
17. Preobrazenskij, P.: Nerve as Resorbable Suture Material, Vestnik. khir. **75-76**: 59-60, 1933.
18. Sidelnikoff, S.: Versuch einer Ausnuetzung der Nabelschnur als Nahtmaterial, Ginek. **2-3**: 122-126, 1935.
19. Sims, J. M.: Silver Sutures in Surgery, New York, 1858, S. S. & W. Wood.
20. Súsruta: Compendium of General Medicine, cited by Hoernle, A. F. R.: Studies in the Medicine of Ancient India, Oxford, 1907.
21. United States Pharmacopoeia, 2nd Suppl., 11th Decennial Revision, Easton, Pa., 1939, Mack Printing Co.
22. Whipple, A. O.: Use of Silk in the Repair of Clean Wounds, Ann. Surg. **98**: 662-671, 1933.
23. Young, S.: An Attempt at a Systematic Reform of the Modern Practice of Adhesion Especially in Relation to the Use and Abuse of the Thread Suture, London, 1808, Mathews & Leigh.
24. Ziegler, P. F.: Textbook on Sutures, Walpole, Mass., 1939, Lewis Mfg. Co.

PROLIFERATING ADENOMA OF THE THYROID

WUCHERNDE STRUMA OF LANGHANS

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SWISS pathologists regard the proliferating adenoma of the thyroid as the most common type of malignant goiter, while American goiter statistics do not even mention it. Either we have failed to recognize this type of goiter as a distinct entity, or it is so rare in our country as not to warrant its separate classification. The present study was undertaken to clarify the discrepancy between Swiss and American goiter statistics and to search a large collection of surgical material for a type of goiter which conforms with Langhans'[9] classical description of wuchernde struma.

MATERIAL AND METHODS

The gross and microscopic findings of all nodular goiters removed during the last 20 years, from 1936 to 1955, were reviewed. Gross specimens, photographs, and microscopic paraffin sections were searched for a type which showed the structure of the wuchernde struma. We found 14 pertinent cases among 206 malignant goiters (7 per cent). The gross and microscopic findings of these 14 cases were tabulated and correlated with the clinical data and the results of follow-up studies.

CASES

Sex and Age.—Of 14 tumors, 10 were observed in women and 4 in men. The ages of the patients ranged from 20 to 59 years at the time of operation. The average age was 45.5 years.

Clinical Symptoms and Duration of Disease.—Our patients had noticed enlargement of the neck for from 3 weeks to 35 years. The average duration of the disease at the time of admission was given as 16.8 years. Only one patient had had a previous operation, 17 years before we saw him. In addition to enlargement of the neck, which was the chief complaint of most patients, 4 had noticed definite loss of weight, 3 shortness of breath with choking sensation, and 3 a rapid increase in the size of a long-standing goiter.

The most frequent clinical diagnosis was solitary adenoma; in only 2 cases was cancer suspected. Four cases were diagnosed as bilateral nodular goiter.

Operation.—In 4 patients bilateral subtotal thyroidectomy was performed, and in 9 cases lobectomy was done. The only patient with recurrent goiter underwent total thyroidectomy. In no instance was radical neck dissection performed; neither was postoperative x-ray nor isotope treatment administered.

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Gross Pathology.—In most of our 14 patients an encapsulated solitary tumor was found; 4 had multiple nodules. The size of these tumors varied between 2.5 and 15 cm. A capsule was present in all cases; it was grossly invaded in three instances, and in one case a tumor thrombus occluded a larger thyroid vein.

The cut surface of these tumors was opaque grayish white to yellowish amber. A central hyaline scar frequently seen by Swiss writers was seen only four times in our material. Cystic degeneration with or without hemorrhage was present in 3 of our cases.

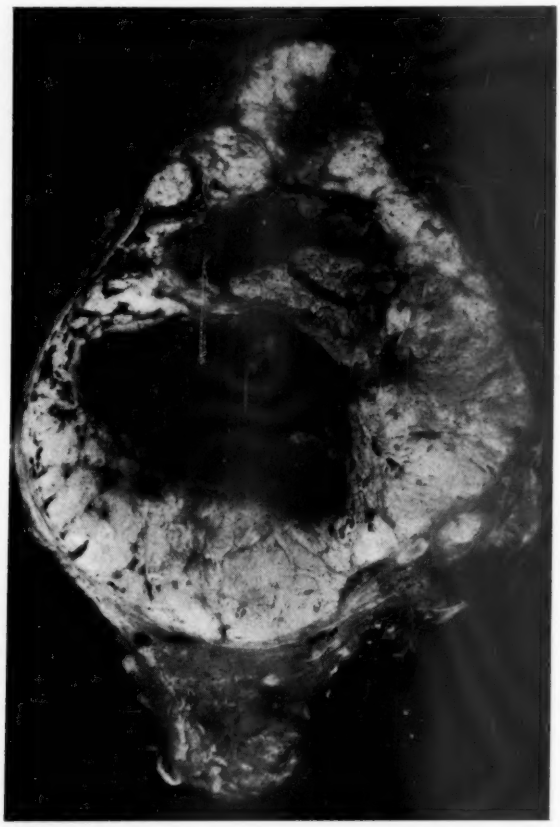

Fig. 1.—Case 4. Proliferating adenoma in 29-year-old man, recurrence of goiter removed 17 years previously.

Microscopic Findings.—Included in this series were only those tumors which showed the two most characteristic morphologic features of wuchernde struma, namely solid broad columns or polygonal masses of tumor cells and wide sinusoids. There was some tendency of the tumors to form small lumina in the central portion.

The width of the solid tumor columns varied in our cases from 5 to 30 cells (between 50 and 300 microns). The cells were cuboid or of polygonal form, seldom columnar, and occasionally oxyphilic. The cell borders were indistinct. There was little variation in the size of the nuclei, and mitotic figures were rare. In 3 cases the capsule and surrounding thyroid tissue were invaded by the tumor cells.

Fig. 2.

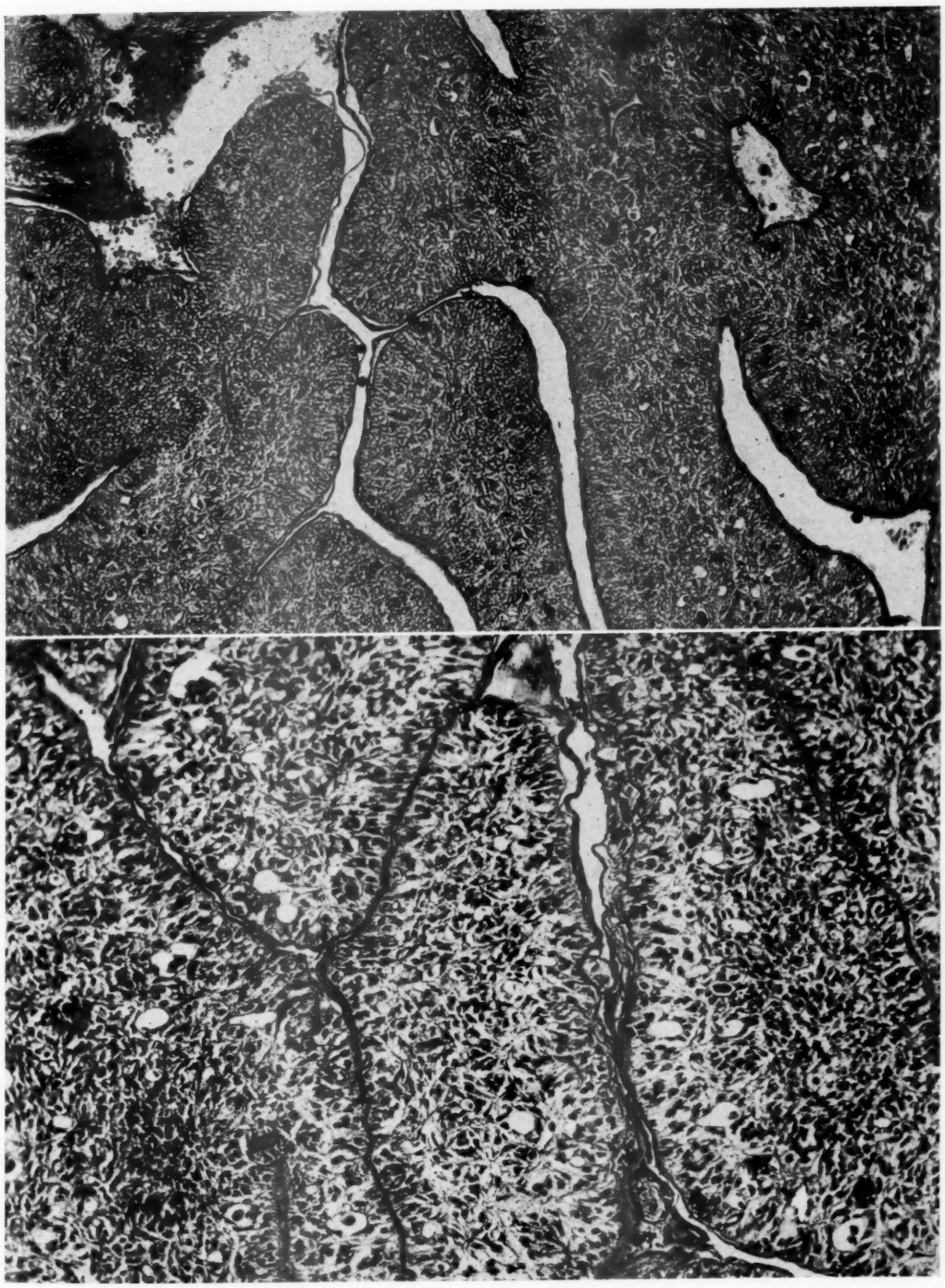

Fig. 3.

Fig. 2.—Photomicrograph of same tumor shows broad columns of tumor cells separated by wide sinusoids.

Fig. 3.—Case 4. High-power photomicrograph. Most of the tumor cells are polygonal, in center of columns. They are columnar and perpendicular to septa. Only few lumens are recognized in the otherwise solid tumor strands.

Follow-up Studies.—The time of observation after operation varied from 7 months to 21 years. At present, 4 of our 14 patients are known to be alive (29 per cent) and without evidence of disease. Two of these patients are well 21 and 22 years after operation. Seven patients have not been heard from, 7 months to 5 years after operation, and are presumed to be dead. One patient died on the sixth postoperative day. Two patients have been operated upon recently and are without evidence of thyroid disease for 18 months and 2 years, respectively.

Characteristic of the slow but often fatal course of this type of tumor is the following case history.

A 29-year-old white man was admitted to the clinic because of a very large recurrent goiter. He had had a goiter operation 17 years previous to this admittance. The recurrent goiter was removed by total thyroidectomy in 1934. Four years later a metastasis developed in the sternum and was treated with deep x-ray therapy. The patient died from the disease in 1943, 11 years after operation for recurrent goiter and 28 years after the first goiter operation.

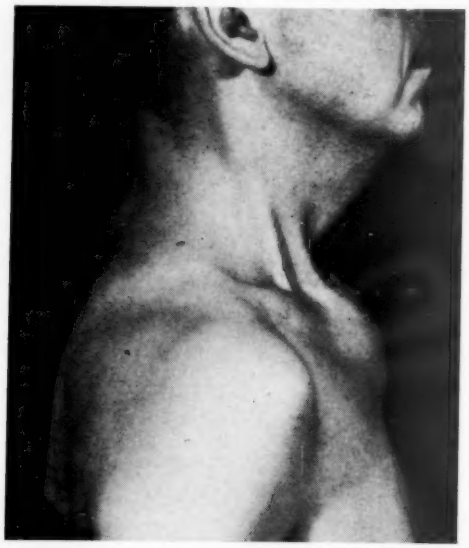

Fig. 4.—Case 4. Metastasis in sternum, 7 years after complete thyroidectomy. Patient died 2 years later of carcinoma. There was no local recurrence or cervical metastasis.

DISCUSSION

Gross Structure.—The proliferating adenoma is a spherical or oval node, 4 to 15 cm. in diameter. Smaller nodes are found occasionally. The surface of the tumor is smooth or flat nodular.

The cut surface is homogenous, light brown to yellow in color, with grayish-white areas. A clear or slightly cloudy thick fluid can be expressed from the tissue. The tumor tissue protrudes over the cut surface of the capsule and surrounding thyroid tissue proper, and its consistency is slightly firmer than that of normal thyroid tissue or benign adenoma. In the center of the node, as a rule, is a fibrous scar which resembles the hyaline-fibrous center of fetal adenoma, except that it has a tougher texture. Not infrequently one sees several nodes more or less separate from each other in the specimen.

Fig. 5.

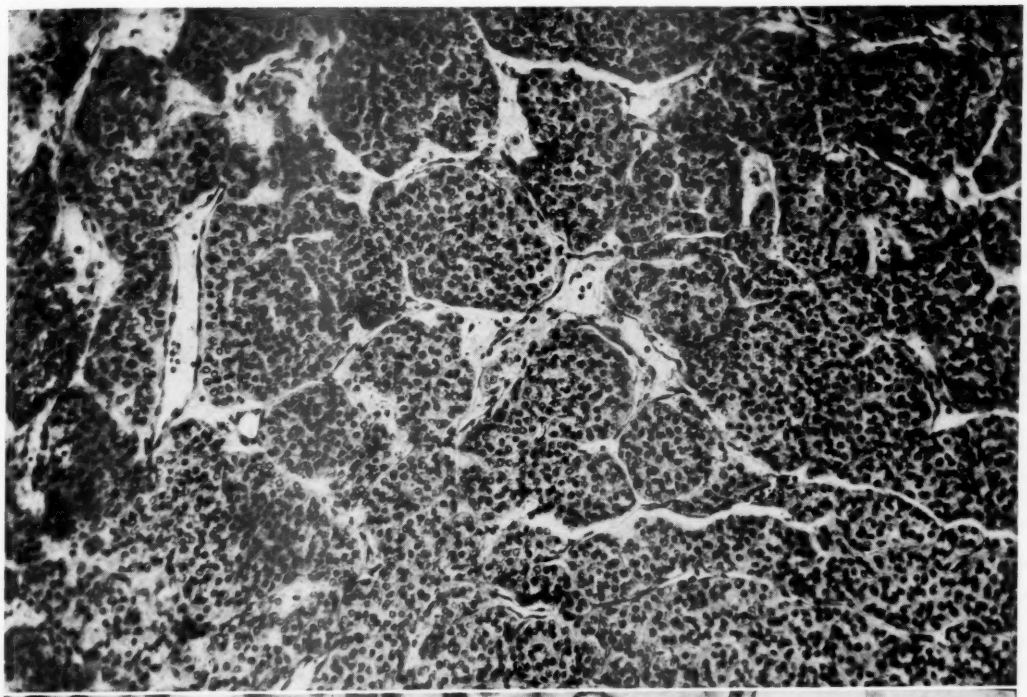

Fig. 6.

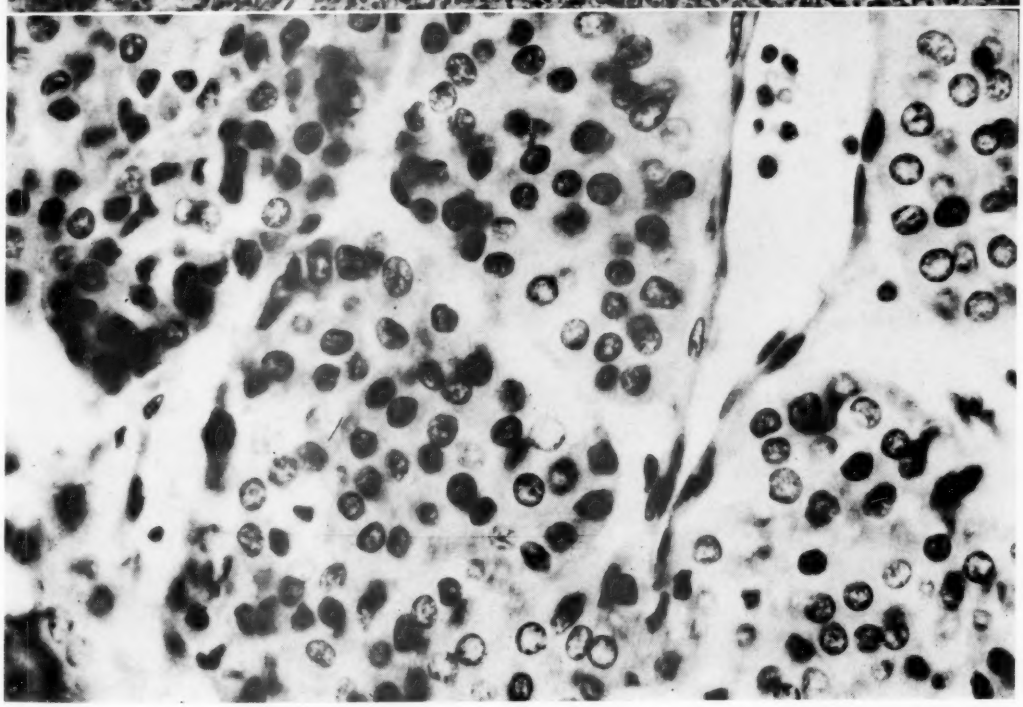

Fig. 5.—Proliferating adenoma showing columns and large polygonal solid cell masses. Wide sinusoids separate the cell groups.

Fig. 6.—High-power photomicrograph of same specimen (Fig. 5) which was taken from metastasis of proliferating adenoma in temporal bone. The close position of the tumor cells to blood sinusoids explains the high incidence of hematogenous metastases.

Microscopic Structure.—The microscopic structure, according to Langhans[9] and Wegelin,[16, 17] is so characteristic that a definite diagnosis can be made from a small piece of tissue. The outstanding features are broad solid columns or polygonal masses of tumor cells and wide sinusoids. The trabeculae are broader than in benign trabecular adenoma. The polyhedral tumor cells have a cloudy fine granular cytoplasm and a vesicular nucleus. Only rarely are multinuclear cells or giant-sized lobulated nuclei seen. Mitotic figures are relatively infrequent. De Quervain[10] saw them in only 6 of his 91 cases. Cell borders as a rule are not visible.

While he found glycogen in most tumors, Wegelin stresses the low fat content of the tumor cells. The tumor cells are arranged in polygonal cell groups or in solid cords running radially to the capsule. The cuboid or polyhedral cells are growing without orderly arrangement in the solid epithelial strands. Near the septa the cells are sometimes columnar and in a perpendicular position to the wall of the sinusoids.

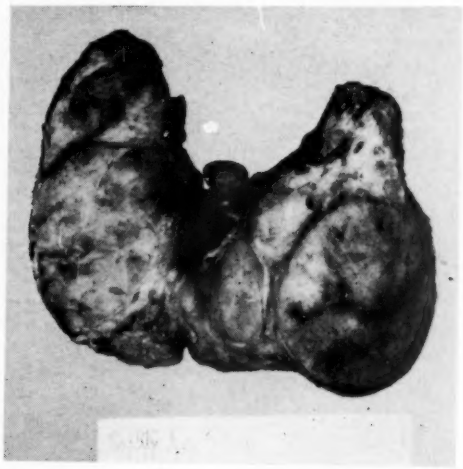

Fig. 7.—Case 14. Typical gross appearance of proliferating adenoma. Circumscribed large node with peripheral lobulation and central scar.

Toward the center of the proliferating adenoma, there is a tendency to form small round lumina in the cell strands. Colloid may finally appear in these lumina and fibrous tissue, and capillaries may grow into the tumor strands from the septa surrounding the follicular structures. As a rule the follicles are scanty, but in some tumors they may be so numerous that a sievelike appearance results.

The wuchernde struma may show, in its microscopic structure, transitions to other goiter types. Donati[4] described border line cases between benign trabecular and proliferating adenoma. In the former, the trabeculae are not so wide and the cells may be arranged in peritheliomatous fashion.

Wegelin described transitions of the wuchernde struma to papilloma and Hürthle cell tumor. Langhans observed in one case a ductlike arrangement of columnar tumor cells. Bircher's[3] 35 cases occurred mostly in younger individuals, and his photomicrographs and morphologic description do not entirely

conform to the Langhans type. For instance, many of his cases did not show the characteristic sinusoids. Barthels[2] therefore questions the diagnosis in many of Bircher's cases.

A history of long-standing goiter is the rule, as is a sudden increase in size. The wuchernde struma appears to originate always in nodular goiter. In 13 of 16 cases of de Quervain, the nodes were parenchymatous; only 3 were microfollicular. Sixty-six per cent of Bircher's cases had their origin in fetal adenoma. Since the latter is the prototype of goiter in highly endemic regions, a high incidence of the wuchernde struma, which is the malignant variant of fetal adenoma, is easily understood.

Fig. 8.—Case 2. Proliferating adenoma of 59-year-old man who had a goiter for 35 years. The tumor measures 15 by 9.5 cm.; it was partly substernal.

Clinical Course.—Langhans in his original paper stated that two-thirds of his 16 cases showed histologic evidence of malignancy. In 3 he saw invasion of the capsule; in 5 the thyroid tissue proper was invaded by tumor cells. In four instances blood vessels were invaded, and 2 patients had metastases in bones and choroid plexus. He never observed lymph-node metastases. Compared with other types of malignant goiter, Langhans regarded the wuchernde struma as the least malignant. Three of his patients died after operation, and there are no other follow-up data in his paper. Of Kocher's[7] cases, several patients died 3½ to 5 years after operation, either from recurrence or metastasis. Of Barthels' 8 patients, 5 died from their disease 3½ to 11 years following thyroidectomy.

Wegelin cited the lungs, pleura, and bones as the most common sites of metastases. The short bones of the trunk and the skull were more often involved than the long bones. De Quervain concluded from the study of 91 cases, observed over a period of 18 years, that long years of survival can be expected after conservative operation. The 5-year survival rate in his cases was 26.4 per cent. He saw metastases in lymph nodes ten times, hematogenous metastases in lungs and bones fourteen times. In several cases extensive tumor thrombi were present in thyroid veins, jugular vein, and superior vena cava. One of his patients had tumor invasion of large blood vessels and survived 7 years after the operation.

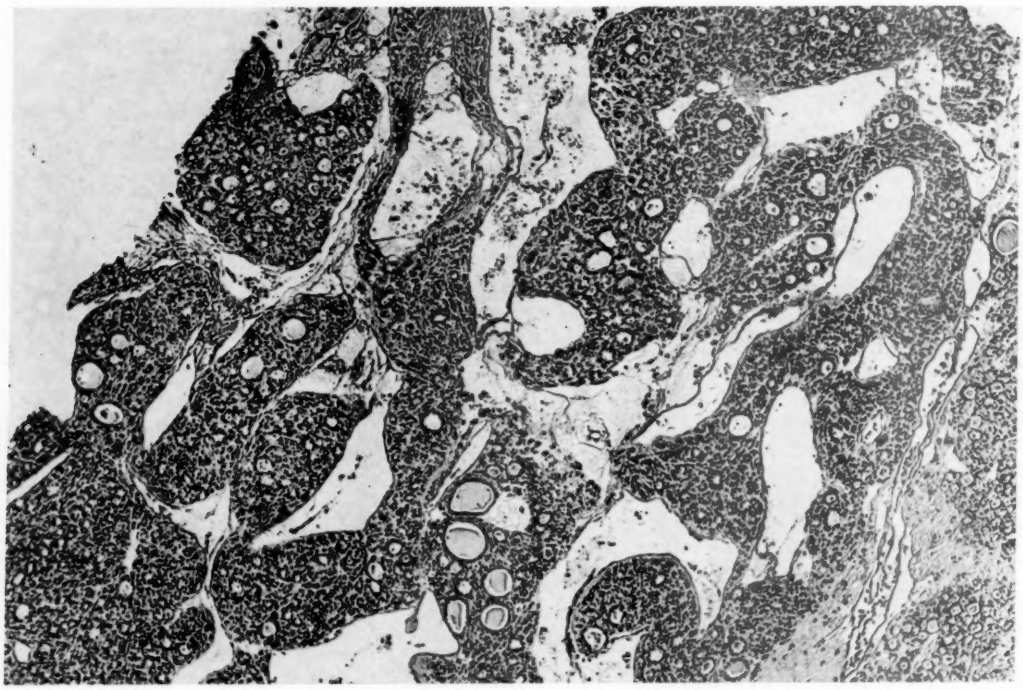

Fig. 9.—Photomicrograph shows broad columns separated by wide sinusoids. There is some tendency to develop follicles.

According to de Quervain, bone metastases may be observed before the primary thyroid tumor has been detected. On the other hand, metastases in bone may occur several years after removal of a thyroid tumor. v. Albertini[1] regards the prognosis of the wuchernde struma as very serious, not better than that of undifferentiated carcinoma.

Herbst,[5] in a clinical survey of malignant adenoma, gives a 5-year survival rate of 17 per cent. He includes, however, in his group of malignant adenomas, not only wuchernde struma, but also follicular carcinoma and adenocarcinoma.

Of Ward's[15] 7 patients, observed among 60 cases of malignant goiter, 4 died of cancer, 2 were alive with recurrence, and only one remained well 4 years after operation.

Literary Review.—The original paper on wuchernde struma by Langhans appeared in 1907 and was based on the study of 16 cases. If one compares his description with the papers written later on the same subject, one is astounded by Langhans' genius in recognizing this special type of goiter and separating it from differentiated cancer types. Writers who studied the same form of goiter during the following 50 years made valuable additional observations, but the essential morphologic data of Langhans have not been altered.

In addition to Langhans' 16 cases, we found reported in the literature the following cases: 7 by Zehbe,[22] 3 by Wolff,[20] 3 by Krompecher,[8] 6 by Wissmer-Kovarsky,[19] and 35 by Bircher.[3] Wegelin, in 1926, summarized the morphologic findings in 31 cases, and de Quervain described the clinical features of 91 cases. Barthels, in 1931, stated that in East Germany, 10 per cent of all malignant goiters showed this structure. Walthard,[14] in a recent survey of Swiss goiters (1955), regarded the proliferating adenoma as the most common type of malignant goiter in Switzerland, accounting for 33 per cent (Thalmann[13]) and 42.5 per cent (Richard[11, 12]) of the malignant goiters.

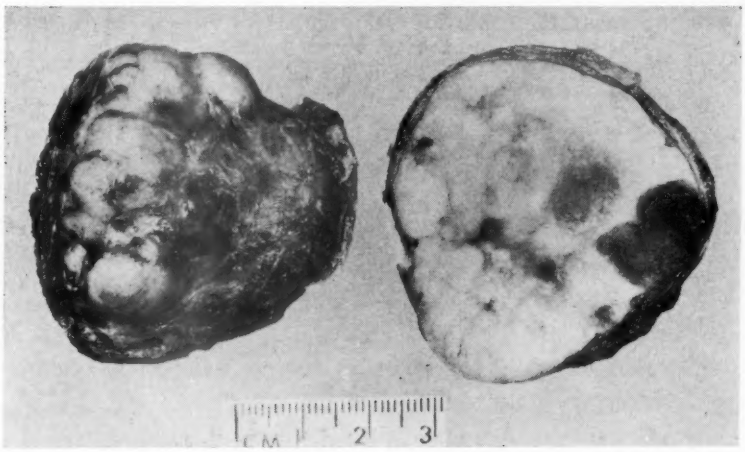

Fig. 10.—Case 13. Proliferating adenoma, 5 cm. in diameter. At right, remnant of benign colloid adenoma in which the tumor developed.

In the American literature two references are found before 1935, while during the last 20 years no mention of proliferating adenoma is made. Wilson,[18] in his excellent review of malignant goiters at the Mayo Clinic in 1921, gave a detailed description of this tumor. He included among his 102 cases of "malignant adenoma" numerous cases of wuchernde struma. His photomicrographs Figs. 36 to 40 are excellent examples of this goiter type. However, Wilson did not state what percentage of his 102 malignant adenomas showed the picture described by Langhans.

The only other American author who studied this goiter type was Ward, in 1935. Thirteen per cent of malignant goiters observed by him in San Francisco showed this structure. By comparing goiter types in Switzerland and North America, he concluded that goiter regions of high endemicity have a large proportion of proliferating adenoma and a low incidence of papilloma. As the

goiter frequency decreases in a country, the proportion of proliferating adenomas also decreases, while that of papillomas increases. He regards the proliferating adenoma as three times more malignant than papilloma, but as less malignant than undifferentiated carcinoma. Ward's view has been substantiated by Thalmann, who in surgical goiter material in Bern, Switzerland, found that, between 1940 and 1950, 33 per cent of the malignant goiters were wuchernde struma compared to 10 per cent papilloma. Another author (Richard[11, 12]) reports from Rorschach, Switzerland, in 1949, a similar relationship, namely, 42.5 per cent wuchernde struma and only 6.3 per cent papilloma. In Vienna, where there is a low incidence of endemic goiter, Zaunbauer[21] in 1952 found among 80 malignant goiters only 8.7 per cent wuchernde struma.

In a recent paper, Horn[6] (1951) deals with a type of goiter which appears to be similar if not identical to wuchernde struma. His 7 cases had a remarkably slow course in spite of solid cell structure. The basic pattern in Horn's cases consisted of sharply defined cell groups. The stroma varied from delicate septa consisting largely of blood vessels to broad bands of dense, sometimes hyaline-fibrous, tissue. The tumor cells were of fairly uniform size, and mitotic figures were generally infrequent. All of Horn's cases showed metastases. The duration after onset of symptoms varied from 2 to 12 years. In spite of its resemblance to the compact solid carcinoma of Lahey and Warren, Horn regards this tumor as a separate entity, because it does not pursue the rapid course of anaplastic thyroid carcinoma.

SUMMARY AND CONCLUSIONS

1. Among 206 malignant goiters observed during 20 years at the Hertzler Clinic, 14 (7 per cent) had the structure of proliferating adenoma (wuchernde struma of Langhans).

2. Ten of the proliferating adenomas were observed in women and 4 in men. The ages ranged from 29 to 59 years.

3. Enlargement of the neck was noticed by these patients for 3 weeks to 35 years. The average duration of the goiter previous to operation was 16.8 years.

4. The most frequent clinical diagnosis before operation was solitary adenoma; in only 2 cases was cancer suspected.

5. Bilateral subtotal thyroidectomy was performed on 4 patients, lobectomy on 9. In no instance was radical neck dissection performed.

6. The size of the tumors varied from 2.5 to 15 cm. A capsule was present in all cases. The capsule was grossly invaded in 3 cases; in one a tumor thrombus occluded a large vein.

7. All 14 tumors showed the characteristic structure of wuchernde struma of Langhans, that is, masses or columns of tumor cells. Between these columns there were only wide sinusoids.

8. Of our 14 patients, 4 are alive and without evidence of disease for more than 5 years; 2 are alive over 21 years after operation. One patient died postoperatively; 2 living patients have been operated upon only recently. The 5-year survival rate in our series is 28.6 per cent.

9. We believe that the recent tendency to simplify the classification of malignant goiter and to distinguish only two or three entities disregards the many variations in structure and clinical behavior of malignant goiter. As in brain tumors or lymphomas, a detailed histologic classification of malignant goiters appears to be necessary to understand their different grades of malignancy and to predict, in a given case, the probable course after operation.

10. From the standpoint of geographic pathology it is of interest that in Switzerland, with its high incidence of endemic goiter, the proliferating adenoma is the most common type of malignant goiter, while in countries with low endemicity this type is so rare that in American statistics it is not listed as a separate entity. Our study confirms the observations of Wilson and Ward, that the proliferating adenoma, while rare, occurs also in North America and shows the same morphologic and clinical features as described by Swiss writers.

REFERENCES

1. v. Albertini, A.: Histologische Geschwulstdiagnostik, Stuttgart, 1955, Georg Thieme, pp. 330-333.
2. Barthels, C.: Struma maligna, Erg. Chir. Orthop. **24**: 162-325, 1931.
3. Bircher, E.: Beiträge zur Kropffrage; die wuchernde Struma Langhans, Beitr. klin. Chir. **139**: 383-420, 1927.
4. Donati, M.: Contributo allo studio dei carcinomi della ghiandola tiroide, Arch. sc. med. **31**: H-2, 1907; Fortschr. Chir., 1907; quoted by Barthels.[2]
5. Herbst, W. P., Jr.: Malignant Tumors of the Thyroid, Ann. Surg. **79**: 488-494, 1924.
6. Horn, R. C., Jr.: Carcinoma of the Thyroid; Description of a Distinctive Morphological Variant and Report of 7 Cases, Cancer **4**: 697-707, 1951.
7. Kocher, T.: Zur klinischen Beurteilung der bösartigen Geshwülste der Schilddrüse, Deutsche Ztschr. Chir. **91**: 197, 1907.
8. Krompecher, E.: Zur vergleichenden Histologie der malignen epithelialen Schilddrüsengeschwülste, Beitr. path. Anat. allg. Path. **73**: 386-403, 1924-1925.
9. Langhans, Theodor: Über die epithelialen Formen der malignen Struma, Virchow's Arch. path. Anat. **189**: 69-188, 1907.
10. de Quervain, F.: Die Struma maligna. Neue Deutsche Chirurgie, Bd. 64, Stuttgart, 1941, Ferdinand Enke, pp. 334-352.
11. Richard, M.: Erfahrungen an 700 Schilddrüsenoperationen, Helvet. chir. acta **20**: 16-36, 1953.
12. Richard, M.: Über die maligna Struma, Praxis **38**: 597-602, 1949.
13. Thalmann, Arnold: Die Häufigkeit der Struma maligna am Berner Pathologischen Institut von 1910-1950 und ihre Beziehung zur Jodprophylaxe des endemischen Kropfes, Schweiz. med. Wchnschr. **84**: 473-478, 1954.
14. Walthard, B.: Formenkreise und Zusammenhänge von Kropf und Krebs, Strahlentherapie (Suppl.) **34**: 69-99; 146-149 (disc.), 1956.
15. Ward, R.: Malignant Goiter; A Survey of Geographical Types, West. J. Surg. **43**: 494-504, 1935.
16. Wegelin, C.: Die Schilddrüse, *in* Henke, F., and Lubarsch, O., editors: Handbuch der speziellen pathologischen Anatomie und Histologie. Achter Band; Drüsen mit innerer Sekretion, Berlin, 1926, Julius Springer, pp. 253-260.
17. Wegelin, C.: Malignant Disease of the Thyroid Gland and Its Relations to Goitre in Man and Animals, Cancer Rev. pp. 297-313, July, 1928.
18. Wilson, L. R.: Malignant Tumors of the Thyroid, Ann. Surg. **74**: 129-184, 1921.
19. Wissmer-Kovarsky, Mme. Xenia: Les tumeurs malignes du corps thyroïde, Rev. méd. de la Suisse Rom., Genève **33**: 815-835, 1913; **34**: 24, 1914.
20. Wolff, G.: Wuchernde Struma; ein Beitrag zur Lehre von den epithelial-bösartigen Geschwülsten der Schilddrüse, Bruns' Beitr. klin. Chir. **121**: 56-57, 1920.
21. Zaunbauer, W.: Wien med. Wchnschr. **50**: 993, 1952. Quoted in Walthard.[14]
22. Zehbe, M.: Bösartige Epithelgeschwülste der Schilddrüse, Virchow's Arch. path. Anat. **197**: 240-290, 1909. Quoted in Walthard.[14]

JUVENILE APONEUROTIC FIBROMAS

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MANY reports regarding Dupuytren's contracture in the hands have resulted in quite universally satisfactory management of this process, while those reports of the fibrous homologue affecting the feet, Dupuytren's fibrous dysplasia or fibromatosis, have not afforded equal appreciation of that lesion and unnecessary amputations have been considered necessary in its control.[8] A more unusual type of fibrous dysplasia is Keasbey's juvenile aponeurotic fibroma.[5] Because of a similar characteristic of infiltrative recurrence, this lesion has occasioned similar radical surgical consideration, 3 out of 4 of Keasbey's patients having been given such a recommendation.

In a previous study of tumors of the hands and feet, only one patient with this tumor was found in an analysis of 502 benign tumors of the hands and feet in a 13-year period of observation.[2] Since only 6 patients have been reported, two classical examples of juvenile aponeurotic fibroma seem worthy of comment, with two other variants of juvenile fibromatosis. We have been interested in this problem of fibrous dysplasia, at first stimulated by this process occurring in the anterior abdominal wall of children.[3]

Bick[1] has previously indicated a tendency for fibromas to arise in the hands and feet in reporting that 21 out of 26 fibromas in his experience arose on the hands and feet. Stout[10] observed that, while connective tissues are practically ubiquitous, overgrowth of fibrous tissue tends to appear much more frequently in some areas than others. He also indicated that there was a high rate of occurrence in these areas, and in 14 out of 44 patients with juvenile fibromatoses in his series, the site of origin was on the hands and feet. In reviewing the problem of extraabdominal desmoid tumors, Musgrove and McDonald[7] reported none arising in these sites. Prior and Sisson[9] in a general review of dermal and fascial fibromatosis have concluded that the entity of infantile fibromatosis is the same lesion known also as dermatofibroma and fibroma duram, but emphasize that the tumor has considerably greater growth potentiality when it occurs in younger age groups. More recently a report of 6 patients with digital neurofibrosarcoma in infancy from the Children's Hospital in Boston has indicated that there is a more malignant tumor of fibroblastic origin in this age group.[4]

In 1953, Keasbey[5] clearly defined the clinical and pathologic entity of juvenile aponeurotic fibroma as a distinctive tumor arising in the palms and soles of young children. She has described what appears to be a benign tumor

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of self-limited growth that nevertheless imparts a histologic impression of cellularity and invasion, and shows a disturbing propensity to recur postoperatively after incomplete excision. She felt it desirable to distinguish these peculiar tumors from fibromas in general. She stated that the growth of tumor cells in these lesions tended to form great sheetlike masses and "their apparent origin from the delicate connective tissue intervening between voluntary muscle cells suggest a neoplastic caricature of aponeurosis formation. The late concentration of the cells into a more solid and discrete tumor resembles the formation of tendon, and in these later tumors the plump type of the fibroblasts and the occurrence of the giant cell areas seen adjacent to foci of calcification bears resemblance to tumors of tendinous origin."

In the 4 patients we are reporting, there are many variables both in the gross and clinical appearance as well as in microscopic detail. In each there is a distinct infiltrating fibromatous process which initially has presented a marked variation in its appearance from its latest most maturated form. Once the lesion seemed most consistent clinically with neurofibromatosis, and yet histologically, no such connection could be construed. Because only small series of such cases have been reported and a decisive definition of tumors of fibromatous origin in these areas has not been entirely possible, a detailed study of 4 patients in our experience seemed indicated.

CASE REPORTS

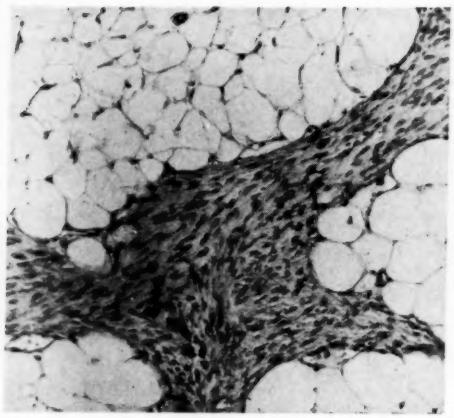
CASE 1.—This child (B. B.) was normal in all respects except for a small tumor on the right wrist which her mother noticed when she was 7 days old. This grew rapidly and measured 3.0 cm. in diameter by the time the child was 2 months old.

At this time the lesion was excised and was said to have arisen from a tendon sheath at the radial side of the volar aspect of the right wrist. It was further described to be friable and unencapsulated. The microscopic diagnosis reported was "lipofibrosarcoma of low grade malignancy." It recurred and again was removed at the age of 6 months. A microscopic diagnosis of "recurrent fibrosarcoma" was made. The child was then referred to the Memorial Hospital in June, 1951, after the question of an amputation had been raised (Fig. 1, *A*). The slide from the second excision was reviewed by Dr. Fred Stewart with the following comment: "Fibrolipoma—in our experience these lesions have never warranted, by their course, the diagnosis of fibrosarcoma. They are peculiar to infancy." (Fig. 1, *B*.)

In brief, between July, 1951, and March, 1953, with Drs. Lemuel Bowden and Isabel Scharnagle, we have made three attempts to remove this tumor, in each instance utilizing a tourniquet technique. We have found this tumor to extend around and between the volar radial tendons and the median nerve, and to the greater multangular and navicular bones as well as the styloid process of the radius.

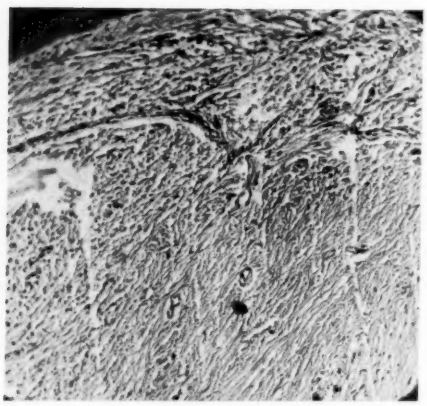
Microscopic interpretations of the successively removed tissue has progressed from fibrolipoma to desmoid (Fig. 1, *C*), and the last two specimens were reported to be tendon fascial fibroma (Fig. 1, *D* and *E*). In 1955, at age 5 years, a firm discrete recurrence was found in the volar aspect of the wrist. X-ray films of the wrist in April, 1955, first showed multiple smudge-like calcifications in this area. This progressed and by May, 1957, there was definite calcific stippling of the soft tissue of the tumor site as shown in Fig. 1, *F*.

This child documents the evolution of this fibrolipomatous tumor with the maturation into a comparatively discrete solitary mass showing a compact fibroma with calcific stippling. Certainly she has been spared an amputation for what at one time was considered to be a fibrosarcoma.



A.

B.



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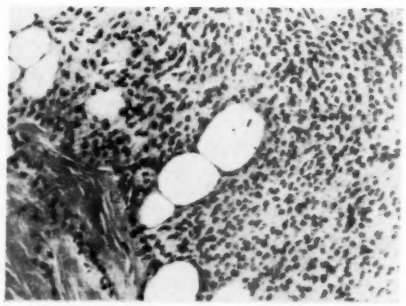

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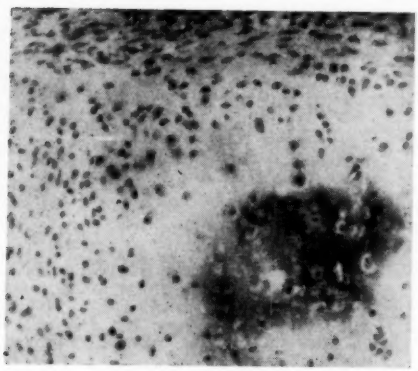
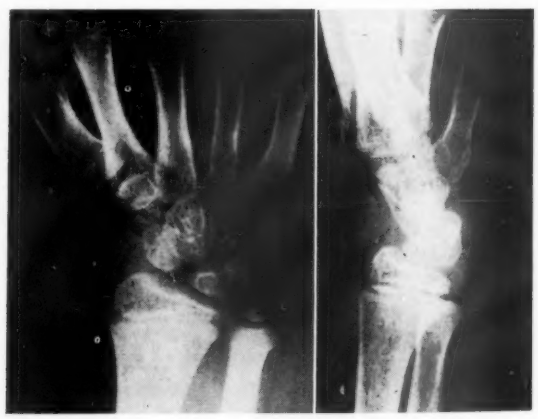


E.



F.

Fig. 1.—*A*, Specimen (×200; reduced 3/7) at time of first excision at age 2 months. The tissue was said to be grossly friable and not encapsulated. This slide shows fibrous tissue made up of spindle-shaped cells in parallel arrangement surrounded by adult fat tissue. Diagnosis: fibrolipoma. *B*, Infant's hand showing a firm nodular recurrence over the radial styloid, at age 11 months. *C*, Tissue resected in the third operation, age 11 months. This is an acellular fibroma similar to an extra-abdominal desmoid tumor. (×75; reduced ⅜.) *D*, Fourth excision, March 10, 1953. This tissue was grossly firm and cartilaginous in consistency. It was considered consistent with a fascial fibroma. The tumor cells are small and oval with slightly more cellularity than is shown in Fig. 1, *A*. (×200; reduced ½.) *E*, Same resection showing focus of calcification. The small oval cells are typical of this type of fibroma. (×400; reduced ½.) *F*, May, 1957, at age 7, multiple fine smudgelike calcifications extending from the base of the first metacarpal to the tip of the radius. Some demineralization of all the bones of the wrist is apparent. A nodule of recurrence was palpable.

CASE 2.—Since birth this otherwise normal child (E. S.) had a soft nontender mass in the palm of his right hand (Fig. 2, *A*). He was first seen in the Mixed Tumor Service in December, 1953, at the age of 5 months. The mass in the palm was compressible and seemed to incorporate the thenar muscles. It infiltrated through the dorsum of the hand through the first interosseus space. An X-ray showed a diffuse prominence of soft tissues of the palm, but did not show the diminished density characteristic of lipoma.

In January, 1954, the distal part of the palm was explored through an incision in the distal palmar crease, utilizing a blood pressure tourniquet technique to establish a bloodless operating field. The neurovascular bundles were dissected free of an edematous yellow fatty tissue (Fig. 2, *B*). The pathologist's report was "lipoma."

In April, 1955, at age 20 months, a dissection of the proximal aspect of the palm was performed through an incision in the thenar crease, removing edematous but firm and desmoplastic yellowish-orange tissue (Fig. 2, *C*). Because of the previous report of the pathology involved, the thenar eminence was not skeletonized free of this tissue at that time. The pathology report was "juvenile aponeurotic fibroma." Two years later the tumor tissue in the thenar eminence was essentially the same size, but had become much more firm in character; it did not show any foci of calcification, however.

CASE 3.—The baby (L. C.) was first seen in the Mixed Tumor Clinic in June, 1954, at the age of 2½ years. She presented the most unusual manifestations of this process. The child was the third born of normal parents; her older siblings were entirely normal. The baby was seen because of deformities of the hands and feet. Her mother stated that the first abnormality was noted at the age of 2 months when a small soft nodule appeared in the central plantar aspect of the metatarsophalangeal area. This deformity slowly expanded until it measured 4.5 by 5.5 cm. and presented a diffuse soft corrugation of the sole as shown in Fig. 3, *A*. At the age of 4 months the left hand began to show an abnormality; the thumb, index, and middle fingers became enlarged and elongated (Fig. 3, *B*). Later a mass was palpable in the upper abdomen and also a prominence appeared in the left pretragal area. At the age of 2 years the right hand became involved in the same process. A biopsy of the abdominal mass was reported to be lipoma.

A skeletal survey showed small exostoses of the proximal phalanges of the index, middle, and ring fingers of the right hand and of the distal phalanges of the corresponding fingers of the left hand. An apparent growth interference of the middle phalanges was manifest by shortening of the phalanges and their increased girth. A large soft tissue mass appeared in the left foot. The clinical picture was suggestive of neurofibromatosis.

Because of continuing slow growth of the plantar tissues of the left foot and increased difficulty in walking, a dissection of the soft tissues of the plantar area was performed in an attempt to remove the bulk of the mass. Nothing more than lipomatous overgrowth was found and so confirmed by the pathologist's report. No relief was obtained and no explanation could be offered on the abnormality.

Due to the continued growth (Fig. 3, *C*), an amputation of the hypertrophied first and second toes of the left foot, with a sacrifice of the greater part of the corrugation of the metatarsal area was performed in February, 1956. The defect was closed by the transference of a pedicle from the dorsum of the toes.

The pathology report described nodular tissues with glistening whitish tissue bulging into the thickened skin, and generalized obliteration of the normal fatty tissue. The diagnosis of juvenile fibromatosis was made. No sign of nerve participation was noted to substantiate a background of neurofibromatosis.

Since that time there has been little change in the process in the feet. The great changes have been in the hands where the interphalangeal joints of the index and middle fingers have virtually become ankylosed. Recent films of the hands show, in addition to the phalangeal exostoses, definite soft tissue calcification as described in the juvenile aponeurotic fibroma (Fig. 3, *D*).

A. *B.* *C.*

Fig. 2.—*A*, Right hand of 6-month-old male infant with a soft compressible mass incorporating the thenar area and distal part of the radial side of the palm. *B*, View at operation through distal palmar crease. A diffuse infiltration of edematous fatty tissue is apparent. *C*, View at operation at age of 20 months through thenar crease approach. The infiltrating tissue was edematous, yellow-orange in color, but firm and desmoplastic. The branches of the median nerve are seen to be engulfed by the tumor.

A. *B.*

C. *D.*

Fig. 3.—*A*, Baby L. C. at age 20 months, showing overgrowth of plantar tissues bilaterally, with a diffuse soft corrugation in the medial side of the left forefoot. *B*, Hands at this time, showing enlargement and lengthening of the index and middle fingers and right thumb. *C*, Feet at 3½ years showing persistence and extension of a firm lobulated overgrowth. *D*, Right index finger at age 6 years. Local calcification of the soft parts enlargement as well as the exostosis-like defects in the distal parts of the proximal and middle phalanges.

Fig. 4.—I. B. at age 27 months showing fibromas of the right ring finger (1.5 by 1 by 0.4 cm.) and index fingers, and smaller lesions on the left index and ring fingers.

CASE 4.—This 27-month-old girl (I. B.) presented a 1.5 by 1 by 0.4 cm. nodule on the radial side of the left ring finger, questionably fixed to the deep structures. Similar but smaller lesions were found on the distal interphalangeal joint of the index and middle fingers, as well as small lesions on the right index and fourth finger, measuring 0.5 and 0.7 cm., respectively. The lesions of the left hand were excised. The skin defect on the left fourth finger was closed by means of a pedicle flap from the abdomen. These were reported to be fascial fibromas. The child died 20 hours postoperatively of an acute tracheobronchitis.

This infant had one lesion of the finger at the age of one year, but five digits were involved at the time of surgery. All of these were fibromas, although they are not of the Keasbey type. We feel the patient is worthy of brief comment, not because of the tragic outcome, but because of the multiplicity of lesions, that is, generalized fibromatosis.

DISCUSSION

Review of these infants with such fibromatous overgrowths bears out Stout's observation that they do not fit into any of the well-known localized or generalized lesions previously described, and emphasizes that in their original manifestations the surgeon or physician has little proper background of experience upon which to base a prognosis or to suggest treatment. The first infant began with a tumor which was initially considered to be a malignant one, and with its original appearance might have merited amputation. As its evolutional pattern has been observed, it is questionable if the numerous surgical procedures have altered the impetus of the tumor and its maturation into a more circumscribed process. Even before Prior and Sisson's report[9] of an 8-year-old girl with a twice-recurrent fibroma of the thumb subsequently treated by amputation and who 7 years later had pneumonectomy performed for a metastasis as typically a benign fibroma as that on the thumb, Keasbey's experience had led her to state that one of her objects in writing up these juvenile aponeurotic fibromas was to give these tumors a name and a definition in the hope that if others have seen more malignant and aggressive individuals of this group, they might be reported as a contradiction of her statement.[5] A more recent experience with a congenital fibrosarcoma by a competent pathologist, but which on examination of all the entire specimen proved to be a fibrosarcoma, indicates that our experience with these variants is far from complete.

The second and third cases present problems at first appearing as variants of a diffuse infiltrating lipomatosis. The second child has subsequently developed an aponeurotic fibroma, and the latter has developed a fibroma that in radiographic follow-up shows the development of focal calcification characteristic of the maturation of these fibromas. The last unfortunate patient indicates a generalized or multiple phase manifestation of juvenile fibromatosis.

In dealing with desmonas of the abdominal wall in both children and adults, after multiple excisions we have completed our last operation with the feeling that the border of resection was precarious. And yet the failure to find recurrences has posed the question of whether we have had a surgical cure or whether the tumor failed to grow further because of loss of growth impetus by some process of maturation.

Our experience epitomizes the observation of Keasbey, and we know of no more reasoned and considered viewpoint of management than quoting her observation to us[6]: "Consequently, I would encourage you to cut through the tumor tissue and dissect out these structures with the hope of eradicating the tumor even in the face of these narrow margins and with the knowledge that amputation is not urgent and could certainly be resorted to later if it proves impossible to control the fibroma without the resection of structures essential to the function of the hand."

SUMMARY

1. The problem of juvenile fibromas of the hands is discussed.

2. Two patients with typical juvenile aponeurotic fibromas are presented with long clinical courses of maturation.

3. Other variants of juvenile fibromas are presented, one of which may yet fulfill the requisites for this category of fibromas.

4. Conservative surgical management is in order.

5. It is suggested that this complexity of infancy may not complete its process of maturation in early childhood and continued observation and reporting of these occasional problems is in order.

We are deeply indebted to Dr. Stephen S. Sternberg in the review of the pathologic tissues involved and for aid in preparation of the photomicrographs, and Dr. Robert S. Sherman for the radiographic studies.

REFERENCES

1. Bick, E. M.: Fibrosarcoma of the Extremities, Ann. Surg. **101**: 759-765, 1935.
2. Booher, R. J., and Pack, G. T.: Unpublished data.
3. Booher, R. J., and Pack, G. T.: Desmomas of the Abdominal Wall in Children, Cancer **4**: 1052-1065, 1951.
4. Jensen, A. R., Morton, L. W., and Longino, L. A.: Digital Neurofibrosarcoma in Infancy, J. Pediat. **51**: 566-570, 1957.
5. Keasbey, L. E.: Juvenile Aponeurotic Fibroma (Calcifying Fibroma). A Distinctive Tumor Arising in the Palms and Soles of Young Children, Cancer **6**: 338-346, 1953.
6. Keasbey, L. E.: Personal communication, 1953.
7. Musgrove, J. E., and McDonald, J. R.: Extraabdominal Desmoid Tumors: Their Differential Diagnosis and Treatment, Arch. Path. **45**: 513-540, 1948.
8. Pickren, J. W., Smith, A. G., Stevenson, T. W., and Stout, A. P.: Fibromatosis of the Plantar Fascia, Cancer **4**: 846-856, 1951.
9. Prior, J. T., and Sisson, B. J.: Dermal and Fascial Fibromatosis. Ann. Surg. **139**: 453-467, 1954.
10. Stout, A. P.: Juvenile Fibromatosis, Cancer **7**: 953-978, 1954.

SUBSTANCES RELEASED FROM THE SKIN FOLLOWING THERMAL INJURY

"Burn Toxin"

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THE existence of a "burn toxin" has been discussed pro and con over the years.[13] The majority opinion is that no true toxin exists.[1, 4, 9, 22] In April, 1958, at the Federation Meetings in Philadelphia, a group of men working experimentally with thermal injury discussed this problem informally at a luncheon and later formally in a series of papers presented before this group. The large majority of those workers in the field agreed that, although fluid, colloid, and salt loss contributed greatly to death in the first 24 to 48 hours after extensive burns, when these elements were compensated for in great measure, death still occurred in a fairly high percentage of such animals or individuals. The fatal outcome could not be explained entirely by the factors mentioned; therefore, some other cause was responsible, most probably a "burn toxin." Of special interest was the paper presented by Fox[11] who, working with monkeys, found that by using the most modern methods of treatment after extensive second degree burns in these animals he could only reduce the mortality slightly and this reduction was not statistically significant. His treatment included whole blood, plasma, serum, antibiotics, salt solution, and so forth. Another paper relevant to the matter under discussion was by Gilmore and Fozzard[6] who showed in dogs that death following burning could not be explained wholly by fluid loss since death would occur before fluid loss was manifest. When fluid loss was compensated for by use of blood, plasma, saline, and so on, they found that a decrease in cardiac output was still manifest. It was their feeling that this decrease in cardiac output could best be explained by some type of "burn toxin."

With the introduction of the in vivo method of collecting diffusates directly from burned skin as described in a previous paper,[10, 15] it became possible to collect large amounts of material that could be assayed and analyzed. By this method it had been shown that appreciable amounts of protein and protein-split products, sugars, salts, histamine, bradykinin, adenyl compounds, and so on were liberated from the skin.[12, 14, 17] The question now arose as to whether or not these substances enter the circulation and, if so, which of these substances, if any, are toxic. The subject of this paper concerns itself with the assay of

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the toxicity and the purification of the diffusates from burned skin. In a subsequent paper it will be shown by a variety of methods, including immunologic ones, that diffusates from burned skin do enter the general circulation.

METHOD OF COLLECTING DIFFUSATES FOR OBTAINING LARGE QUANTITIES OF MATERIAL

Sprague-Dawley rats weighing approximately 100 Gm. were anesthetized with Nembutal, and dorsal subcutaneous air pockets were made by injecting 30 ml. of air with a 24- to 26-gauge needle and a 30 ml. syringe. By holding the animal by its feet, the skin over the pockets was immersed in a water bath at the desired temperature for designated lengths of time. This provided a method for burning only the skin without damaging the underlying muscles. These burned rats were then suspended by their feet with the dorsal pockets down. Five milliliters of triple-distilled water was injected into the pocket and gently shaken over the inner surface of the burned skin. Care was taken that the fluid came in contact only with the undersurface of the skin involved. After 5 minutes this water was removed and another 5 ml. was injected into the pocket. This procedure was repeated 20 to 25 times over a period of 2 hours immediately following the burning of the skin. This fluid contained the diffusible materials from the burned skin. Following collection, the fluid either was placed immediately in an ice bath or was frozen by immersing the container in a mixture of dry ice and alcohol. Throughout the procedure extreme care was exercised to reduce bacterial contamination to a minimum. All instruments, glassware, and the like were sterilized before use, as was the injected water. The collected material was lyophilized and stored at approximately 5° C. In these studies the temperature of the water was 96° C. and the time of immersion was 15 seconds.

The use of distilled water for perfusion instead of physiologic salt solutions was decided upon because the amount of diffusible material is small in comparison to the salts present in the latter fluids. Since skin burned at 96° C. for 15 seconds is relatively nonviable, there was no objection to using water in such instances. As will be discussed later, such diffusible substances as histamine and proteins were more or less similar when using Ringer-Locke's solution or water. However, the use of water in nonburned animals introduces a form of injury since viable tissues are subjected to hypotonic solutions. That this is the case was demonstrated by the fact that subcutaneous pockets of normal animals perfused with water yielded histamine and protein in appreciable amounts whereas when such pockets were perfused with Tyrode's solution, little of these materials was recovered; therefore, there are no true controls for this experiment. However, since uninjured tissue does not break down and enter the circulation, the lack of true controls is not critical. Nevertheless, burned animals were compared with nonburned animals. Both groups were treated exactly the same way except for the burning. Throughout the study a comparison will be made between the two different types of injury, one by thermal means and the other by hypotonic solutions.

RESULTS

In over 400 animals burned or not burned the average yield of dry material from each animal perfused for 2 hours at 5-minute intervals was approximately 30 mg. per animal. There was no appreciable difference between the burned and nonburned animals. The collection during the first hour was kept separate from the collection during the second hour. The amount of material by dry weight was similar in the first hour and second hour in both groups of animals.

Nitrogen and Protein Determinations.—Table I lists the total nitrogen, nonprotein nitrogen, and protein nitrogen determined on lyophilized diffusates from burned and nonburned animals by standard procedures. This was determined for both the first and second hour of collection. The protein nitrogen and the protein were the same for the nonburned and burned animals during the first hour samples, but increased appreciably in the burned samples collected during the second hour.

TABLE I. NITROGEN AND PROTEIN DETERMINATIONS FOR NONBURNED AND BURNED DIFFUSATE SAMPLES*

	TOTAL NITROGEN (MCG./MG.)	NONPROTEIN NITROGEN (MCG./MG.)	PROTEIN NITROGEN (MCG./MG.)	PROTEIN (MCG./MG.)
Nonburned, first hour	47.0	7.20	39.8	0.25
Nonburned, second hour	47.0	7.90	39.1	0.24
Burned, first hour	48.1	7.16	40.94	0.26
Burned, second hour	80.6	7.74	72.86	0.45

*All collected in triple-distilled water.

Histamine, Bradykinin, and Adenyl Compounds.—The pharmacologic activity of these compounds will be described in a later paper. Briefly, using smooth muscle biologic assay methods,[12, 15, 17] it was found that there was approximately 1.2 to 1.4 mcg. per milligram of histamine in the crude dried material from burn perfusate. In the dried and stored material there was very little bradykinin (from zero to 0.125 mcg. per milligram). The fresh material contained much larger amounts up to 1 mcg. per milligram. There was up to 20 mcg. per milligram of adenyl compounds (adenosine was used as standard material). The rat's blood pressure and the hen's rectal cecum were used for biologic assay.

Salt Content.—In Table II the salt concentration of various crude and partially purified diffusates is presented (sodium, potassium, calcium, and phosphorus). The most significant differences between the burned and nonburned samples are that there were more potassium and phosphorus in the burned than the nonburned samples. This held true for the crude as well as the dialyzed ethanol precipitated material. The method of purification will be described.

The sodium and potassium were determined by flame photometry and calcium was determined by the conventional titrimetric methods.[3] Phosphorus was

TABLE II. ANALYTICAL RESULTS FOR SOME OF THE FRACTIONS INVOLVED IN THE PREPARATION OF THE "BURN TOXIN"*

FRACTION	Na	K	Ca	P (TOTAL)	HEXOSE	RIBOSE
Crude						
Burned	80	90	20	19.3	7.3	
Nonburned	170	30	20	8.2	3.1	
Nondialyzable						
Burned	8	2	70	3.5	11.9	
Nonburned	5	1	20	5.9	14.9	
Dialyzable						
Burned	130	100	3	21.4	5.7	
Ethanol soluble						
Burned	170	70	6	2.3	3.2	
Nonburned	340	60	20	0.4	1.4	
Ethanol precipitate						
Burned	460	40	50	123.5	20.8	3.1
Nonburned	460	10	50			
Charcoal I						
Burned				148.0		1.9
Charcoal II						
Burned				2.5		7.4

*All values in the table are recorded as micrograms per milligram (dry weight) of the fraction.

No detectable desoxyribose was found in the ethanol precipitate fraction (burned) or in the charcoal I and II fractions.

determined first by digesting a sample and then by comparing the optical density at 780 in Beckman spectrophotometer against a standard phosphorus solution.[5] From these determinations it is noted that of the crude burned material, approximately 8 per cent of the dried powder was sodium, 9 per cent potassium, 2 per cent calcium, and approximately 2 per cent phosphorus.

Miscellaneous.—Hexoses were determined by the orcinol method.[21] It was found that there was 7.3 meg. per milligram of dry weight of hexose in the crude burned material compared to 3.1 meg. per milligram of dry weight of the nonburned material.

TOXICITY STUDIES

Rats.—

Acute: The lyophilized material was dissolved in water or 0.9 per cent sodium chloride and injected subcutaneously in small rats. Controls consisted of injecting equal volumes of 0.9 per cent sodium chloride, concentrated hemoglobin, or concentrated skin extracts. The latter two were given in amounts of protein equivalent as determined on the Beckman spectrophotometer. The results of these preliminary studies are given in Table III. It will be noted that when animals weighing 30 to 50 Gm. were given 7 to 12 mg. of protein equivalent per gram per animal, death occurred anywhere from 2 to 5 hours after the injection. With smaller doses the animal became prostrate after 2 hours or more but recovered. With the larger doses they always became prostrate in one hour or more following injection and remained so until they died. The control animals showed no symptoms and did not die within the 5 to 7 hours of observation. Thus the average lethal dose for the rat subcutaneously is approximately 10 mg. of protein per gram or 17 mg. per gram of crude since

TABLE III. EFFECTS OF DIFFUSATES FROM BURNED SKIN IN NORMAL RATS

EXPERIMENT	TOTAL AMOUNT (MG.)	ANIMAL WEIGHT (GM.)	MG./GM. WEIGHT	RESULTS		
				IMMEDIATE	TYPE REACTION AND TIME	END RESULT AT 5 TO 7 HR.
1	108.0	34.6	3.1	±	Prostrate 2 hr.	Survived
2	131.8	33.7	3.9	-	Marked decrease in activity	Survived
3	210.0	33.0	6.4	-	Prostrate 6 hr.	Survived
4	210.0	33.0	6.4	+	Difficulty in locomotion	Survived
5	210.0	27.0	6.8	±	Prostrate 2 hr.	Survived
6	283.0	?	?	-	Prostrate 2 hr.	Died—5 hr.
7	246.0	33.1	7.5	-	Prostrate 1½ hr.	Died—2½ hr.
8	436.0	31.5	9.6	-	Prostrate 1 hr.	Died—2 hr.
9	406.0	35.7	11.4	±	Prostrate 40 min.	Died—3 hr.
10	597.0	50.2	11.9	+	Prostrate 1 hr.	Died—3 hr.

each 100 mg. of crude contains approximately 60 mg. of protein. The intraperitoneal dose for rats (23 to 45 Gm.) is approximately 5 mg. per gram. Similar doses of burned skin suspensions or normal skin cause no reaction whatsoever in these rats.

Chronic: Rats weighing 150 to 200 Gm. were injected with a mixture of rat erythrocytes plus burned diffusates. Approximately 2.5 mg. of washed red cells was incubated with 100 mg. of crude material in 2.5 ml. of Ringer-Locke's solution for 30 minutes at room temperature and the mixture was inoculated subcutaneously in the animals three times a week. This experiment was done primarily to produce hemolytic anemia. As controls, rats were injected subcutaneously with erythrocytes alone. Six rats inoculated with toxin and 2 rats inoculated with red cells alone were followed over a period of time. After 2½ to 3 weeks, when approximately 600 to 700 mg. of the crude dried material had been injected into each of 6 rats, the animals all died. In 2 of the animals the toxin was boiled before use so that there could be no question of introducing infection. Postmortem examination and microscopic sections were done and will be described elsewhere. Except for enlarged spleen, there was no gross pathology noted. Microscopic sections will be reported in another paper. The erythrocyte-injected animals remained normal.

Mice.—Since mice are smaller animals and less material is necessary, these animals were chosen for testing toxicity. It was soon learned that subcutaneously approximately the same dosage per gram of animal was needed for the mouse as for the rat, that is, approximately 15 to 20 mg. per gram of the dried crude diffusate was equal to one lethal dose. Intravenously, 0.6 mg. per gram was the dose necessary to kill a mouse. It should be stated, however, that the dry crude diffusate is not completely soluble in water and that the doses given represent the soluble portion after incubation for one hour at incubator temperatures. The amount of insoluble material will vary depending on the experiment. As much as 50 per cent or more of the material may remain insoluble after incubation with water or saline. Boiling of this dissolved diffusate does not reduce its toxicity.

Since the amount of salt present as well as histamine in a lethal dose is relatively high, the question arose whether or not these factors might be the cause of death of the animal. In Table IV is given the amount of such material in one lethal dose given subcutaneously to a 16 to 20 Gm. mouse. Likewise, various doses of histamine, sodium chloride, potassium chloride, copper, and variation of pH are listed and the effect on mice is noted. The amount of sodium chloride, potassium chloride, and histamine present in one lethal dose of the diffusate is far below the lethal dose for these substances. It will be noted that substances of pH 10.5 to 2.2 have no effect on mice whereas solutions of pH of 1.0 are lethal. The pH of the diffusate was about 7.0 to 7.5. Intracerebral and intravenous injection of salts will be discussed.

TABLE IV. TEST OF LETHALITY OF SUBSTANCES IN BURN DIFFUSATE ADMINISTERED SUBCUTANEOUSLY IN MOUSE

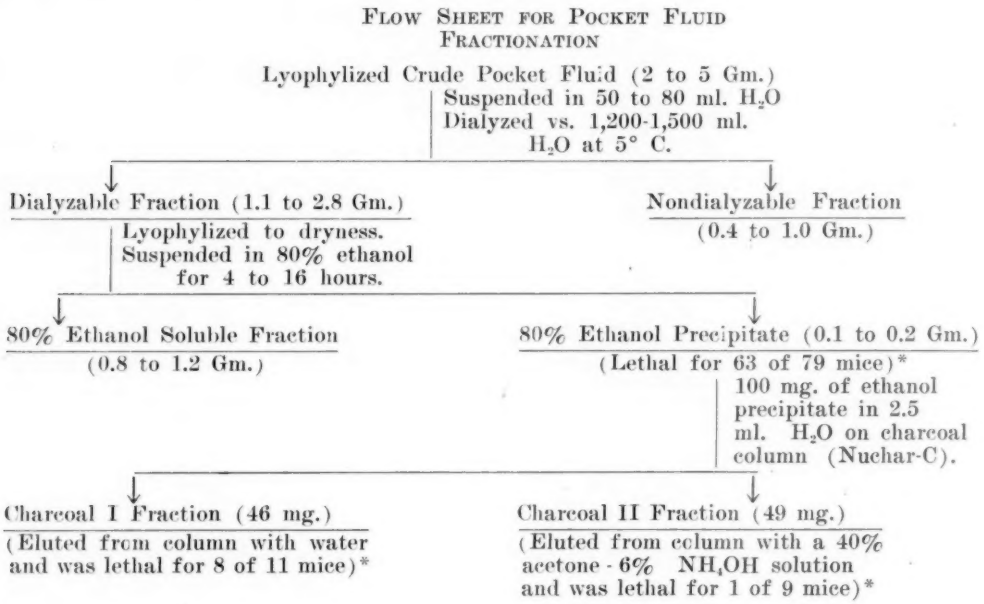
AMOUNT IN ONE LETHAL DOSE* (MG.)		HISTAMINE (MG.)	NaCl (MG.)	KCl (MG.)	Cu (MG.)	pH
Histamine	0.1	0.1–	58–	24–	5+	10.5–
	0.3	1.0–	92±	37+	10+	2.2–
NaCl	4.4	10.0–	145+	74+	20+	1.0+
KCl	1.9	50.0+	178+			
		80.0+	197+			
		100.0+	357+			
			714+			

*16 to 20 Gm. mouse.
-No Effect.
+Lethal.

FRACTIONATION OF DIFFUSATES AND TOXICITY STUDIES

A sample from 2 to 5 Gm. of the lyophilized crude pocket fluid was dissolved in 50 to 80 ml. of triple-distilled water and was filtered to remove insoluble material. The filtrate was dialyzed against 1,200 to 1,500 ml. of triple-distilled water for a dialysis period of 18 to 24 hours in a cold room (5° C.). The dialysis was repeated a second time using a fresh amount of distilled water. The dialysate was concentrated by lyophilization. The nondialyzable material was lyophilized to dryness and stored in the refrigerator. Approximately 20 per cent of the crude material was nondialyzable. Lyophilized dialyzable material was dissolved in triple-distilled water and sufficient 95 per cent ethanol was added to make the final solution 80 per cent ethanol. The addition of ethanol in this concentration (80 per cent) resulted in the formation of a tan-white homogeneous insoluble fraction. After standing for several hours in the refrigerator, the 80 per cent ethanol-insoluble fraction (hereafter referred to as the ETOH-PPT) was recovered by centrifugation and dried by lyophilization. The 80 per cent ethanol soluble fractions were dried in vacuo at 50° C. and by lyophilization and stored in the refrigerator for further studies. In no case was a full recovery of the ETOH-PPT achieved due to the difficulty in transferring the ETOH-PPT which adhered to the wall of the precipitating vessel and to the centrifuge tube. A rough estimate of the amount recovered (expressed as per cent by weight of the starting crude sample) is 1.3 per cent for the nonburned control and 4.5 per cent for the burned samples.

As will be noted from the flow sheet (Fig. 1), the yield of material after fractionation is relatively small especially if many animals are to be used for testing the toxic effects of these fractions. It is for this reason that the intracerebral route in mice was chosen. This is a very exacting method and can be erratic even in experienced hands. Once the technique is mastered, however, the results are fairly consistent. New 26-gauge needles with one-quarter inch stems are used. A new needle is used for every 5 to 10 mice. The syringes should be of 0.25 ml. capacity and graduated in 0.01 ml. divisions. An assistant holds the mouse (16 to 20 Gm.) by the nape of the neck and by the tail and


Flow Sheet for Pocket Fluid Fractionation
Lyophylized Crude Pocket Fluid (2 to 5 Gm.)
Suspended in 50 to 80 ml. H2O
Dialyzed vs. 1,200-1,500 ml. H2O at 5° C.
Dialyzable Fraction (1.1 to 2.8 Gm.)
Nondialyzable Fraction (0.4 to 1.0 Gm.)
Lyophylized to dryness.
Suspended in 80% ethanol for 4 to 16 hours.
80% Ethanol Soluble Fraction (0.8 to 1.2 Gm.)
80% Ethanol Precipitate (0.1 to 0.2 Gm.) (Lethal for 63 of 79 mice)*
100 mg. of ethanol precipitate in 2.5 ml. H2O on charcoal column (Nuchar-C).
Charcoal I Fraction (46 mg.) (Eluted from column with water and was lethal for 8 of 11 mice)*
Charcoal II Fraction (49 mg.) (Eluted from column with a 40% acetone - 6% NH4OH solution and was lethal for 1 of 9 mice)*

* All tests for toxicity were done by injecting 0.03 ml. of the various solutions intracerebrally into 18 to 22 Gm. mice. The concentrations used were: ethanol precipitate, 40 mg. per milliliter; charcoal I fraction, 18.4 mg. per milliliter; charcoal II fraction, 46 mg. per milliliter.

Fig. 1.

places its ventral surface flat and squarely on a table or board. The needle is inserted 2 mm. over the left eye at a 45 degree angle to the table and directed beneath the vortex of the skull. The needle should enter the skull with ease for a distance of about 3 mm. The solution (0.03 ml.) is slowly injected. In a properly executed injection no fluid or blood should issue from the nose or mouth. At the start of each series of injections at least 5 mice should be injected with 0.9 per cent saline from which there should be little to no reaction with complete recovery. On rare occasions one animal may die. The majority of the toxicity studies were done by the intracerebral method. This was further verified by using the intravenous route on a more limited number of animals.

The method of extraction as depicted in the flow sheet (Fig. 1) was repeated on numerous occasions and toxicity tests were run at different times.

The yield, the solubility, and the toxicity were not always constant. The following are three of the series in which fractionation and toxicity studies were made as well as other chemical analyses:

Series I.—

A. Saline: 0.03 ml.: 10 mice injected—1 died, 9 lived.

B. ETOH-PPT:

1. Nonburned precipitate: 20 mg. per milliliter; 0.03 ml.: 9 mice injected—2 died, 7 lived.
2. Burned precipitate:

First hour after burn: 20 mg. per milliliter: 6 mice injected—5 died, 1 lived; 10 mg. per milliliter: 4 mice injected—3 died, 1 lived.
Second hour after burn: 20 mg. per milliliter: 9 mice injected—8 died, 1 lived; 7 mg. per milliliter: 8 mice injected—2 died, 6 lived; 7 mg. per milliliter as above in HCl to pH of 2.0 with more precipitate going into solution: 4 animals injected—4 died, none lived.

All precipitates were taken up in triple-distilled water and incubated for one-half hour at room or incubator temperature. The once precipitated ethanol precipitate as given above was cloudy on resuspension, light tan to gray white in color. Up to 55 per cent of this material did not go into solution. The above experiments indicate that the nonburned precipitate is slightly toxic but only a fraction of that of the burned ethanol precipitate. This experiment also indicates that the toxic principle is poorly soluble in water. As little as 0.2 mg. will kill a 16 to 20 Gm. mouse.

Series II.—The same procedure was followed for fractionation as in Series I and is shown in the flow sheet (Fig. 1) except that the ethanol precipitate was reprecipitated with 80 per cent ethanol. These solutions taken up at 40 mg. per milliliter in water were colorless, clear, or faintly tinted in appearance. The pH of these solutions was neutral or faintly alkaline (pH 7.0 to 8.5). In these studies a concentration of 40 mg. per milliliter (0.03 ml. injected) was necessary to cause death of the animal. As will be seen in the flow sheet (Fig. 1), 63 of 79 mice thus injected died.

Further fractionation of the ethanol precipitate was as follows. Charcoal columns were prepared and exhaustively washed with water, hydrochloric acid, and NH_4OH-acetone solutions. These washings were found to be nontoxic when injected as fairly concentrated solutions intracerebrally into mice. A solution of ethanol precipitate was passed through the charcoal column, eluted with water, and lyophilized. This fraction was called charcoal I fraction. Further elution of the column with NH_4OH-acetone water resulted in a fraction which was dried by lyophilization and was called the charcoal II fraction. Toxicity studies with the charcoal I fraction killed 14 of 18 mice tested. The charcoal II fraction killed only one of 13 mice tested.

The amount of the charcoal I and II fractions injected in the toxicity studies was based on the recoveries and starting weight of the ethanol precipitate put on the charcoal column. The number of lethal doses in the ethanol precipitate used was calculated and it was assumed that all the lethal doses in the ethanol precipitate would be found in one of the two fractions separated on the charcoal column. Each fraction was diluted to the volume in which the original ethanol precipitate had been shown to be toxic. Actually in some tests of the charcoal II fraction a concentration twice that calculated was used and even this level of the charcoal II fraction was not lethal.

Series III.—Three grams of crude burn material was fractionated as in the other series and the toxicity was tested at each stage of purification.

A. Saline: 5 mice injected—all lived.

B. Crude dialysate: 150 mg. in 1 ml. H_2O; 0.03 ml.: 6 mice injected—3 died, 3 lived. 75 mg. per milliliter: 4 mice injected—all lived.

C. Alcohol supernatant: 150 mg. suspended in 1 ml. H_2O; 0.03 ml.: 6 animals injected—3 died, 3 lived.

D. Alcohol precipitates: 40 mg. per milliliter; 0.03 ml.: 4 animals injected—4 died. 20 mg. per milliliter: 6 injected—3 died, 3 lived.

Thus, LD_{50} in this series is approximately 0.03 ml. of a 150 mg. per milliliter solution for the dialysate and for the alcohol supernatant or 0.03 ml. of a 20 mg. per milliliter solution of recrystallized alcohol precipitate.

In the above fractionation the 3 Gm. of crude burn material yielded 1.85 Gm. of dialysate. One gram of this dialysate yielded 0.8 Gm. of supernatant and 109 mg. of recrystallized alcohol precipitate. Assuming that $\frac{1}{LD_{50}} =$ one unit, dialysate and alcohol supernatant have 0.67 unit per milligram and the alcohol precipitate has 1.67 units per milligram. Therefore the total activity in dialysate fraction equals 670 units. Total activity in supernatant is approximately 536 units (0.8 Gm. $\times$ 0.67). Total activity for alcohol precipitate equals 182 units (109 mg. $\times$ 1.67 units per milligram). These data show that full recovery after purification is not obtained; however, they do show that the alcohol precipitate only recovers about 27 per cent of original activity with only about two and a half times' increase in concentration of the active material. They also indicated that the supernatant contains a high percentage of the total activity.

INTRAVENOUS TOXICITY

The lethal dose for the crude toxin for an 18 to 20 Gm. mouse varied from 8 to 12 mg. of the solute contained in 0.1 ml. of fluid after incubation for a half hour at room temperature or at 37° C. and centrifuged. Forty-five milligrams of the nonburned diffusate killed the mouse but 25 mg. produced no symptoms. After dialysis the material (burned) inside the bag was not toxic. On the other hand, the burn dialysate was lethal to the solute from 10 mg.; 22 mg. of the nonburned material was not lethal but 78 mg. was the LD_{50}.

The symptoms following the intravenous injection were similar in most respects to those produced following intracerebral injection of the burned diffusates except for delay of a few seconds. When the material was given intravenously, approximately 5 to 30 seconds after injection the mouse hyperextended its paws and manifested clonic and tonic movements of the extremities. The bladder emptied and the breathing became markedly increased. This was followed by an arrest of breathing although the heart continued to beat for a minute or two at which time the animal either died or slow, deep respirations began which eventually increased until recovery would occur in 5 to as long as 60 minutes after the inoculation.

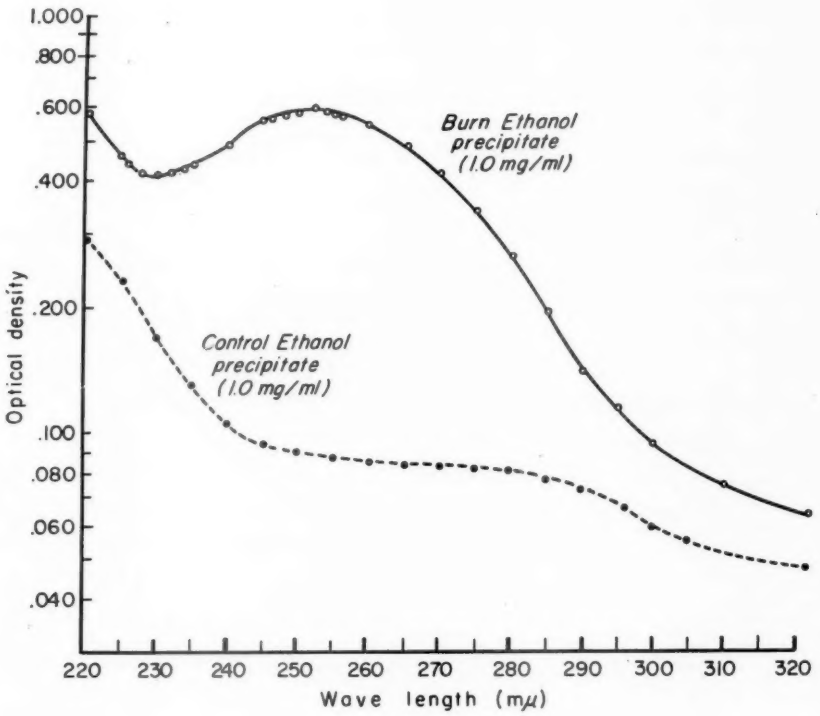


Fig. 2.

CHEMICAL AND BIOLOGIC ANALYSIS OF VARIOUS FRACTIONS OF THE "BURN TOXIN"

Spectrophotometric studies of a solution of the burned ETOH-PPT at pH 2.0 (1 mg. per milliliter) showed a fairly strong ultraviolet absorbing peak at 252 mμ. Similar studies with the nonburned ETOH-PPT at the same concentration showed no ultraviolet absorbing peaks (Fig. 2). The salt and sugar concentration of the various fractions is given in Table II. It will be noted that there is a relatively high percentage of potassium and phosphorus in most of the burn fractions. The hexose content of the ethanol precipitate of the burned diffusate was relatively high.

Tests for histamine, bradykinin, and adenyl compounds will be described in a separate paper.[12] It is of interest that there was no histamine in the

ethanol precipitate, but most of it remained in the supernatant and only small amounts were inside the dialysis bag. There was no bradykinin (or trace amounts at best) in the ethanol precipitate or the ethanol supernatant. However, it is to be recalled that this material was gathered over a long period of time and that bradykinin may have been destroyed in the storage. Adenyl compounds as tested on the rat's blood pressure and the hen's rectal cecum indicated that the highest concentration of this material was found in the crude diffusate and the ethanol precipitate especially after the second precipitation. There were no adenyl compounds left inside the bag.

The ethanol precipitate contained no free purines or pyrimidines (paper chromatography with butanol-H_2O solvent). No free nucleotides (paper ionophoresis using NH_4NCOOH buffer at pH 4.0 and 400 volts across paper) were found as determined by the ninhydrin reaction. However, after hydrolysis with 1N hydrochloric acid, peptides were recovered. No free amino acids were noted but after hydrolysis two ultraviolet spots were noted on ionophoresis having mobilities of cytidylic and adenylic acid.

A number of standard qualitative chemical tests were run on the burn fluid dialysate. The results were as follows: small amounts of desoxypentose sugars (diphenylamine); carbohydrate (Molish); reducing sugars (Benedicts); reducing monosaccharides (Barfoed); no tryptophane (Hopkins-Cole); no SH group (nitroprusside).

TOXICITY OF SALTS AND OTHER PHARMACOLOGIC MATERIALS PRESENT IN THE DIFFUSATES

Salt Mixtures.—A salt mixture was made up of 32 mg. KH_2PO_4, 166 mg. Na_2HPO_4, 12 mg. H_2O, and 180 mg. NaCl, all in 5 ml. H_2O. This salt solution contained then 75 mg. per milliliter salt. When 0.03 ml. was injected intracerebrally, only 1 out of 5 animals died. In other words, 2.5 mg. salt intracerebrally was nonfatal. When 0.2 ml. of this salt mixture, that is, 15 mg. salt, was injected intravenously, it produced no visible reaction whatsoever in 20 mg. mice.

Because the ethanol precipitate contained approximately 123 mcg. per milligram dry weight of phosphorus, the possibility of phosphorus contributing to the cause of death of the animals was considered. A solution of NaH_2PO_4 was prepared so that 200 mg. of phosphorus was contained in each 10 ml. of solution. The solution also contained 148 mg. of sodium per 10 ml.; 0.03 ml. of this material was injected intracerebrally. As is usual, the first 5 mice injected with physiologic saline all lived. Five mice from each group injected with 5, 7.5, 10, and 20 mg. of phosphorus and the corresponding 3.7, 5.55, 7.4, and 14.8 of sodium all lived.

Another approach to the role of salt mixtures in toxicity was to examine the effect of crude "burn toxin" in a living preparation normally existing in salt water such as arbacia eggs.* After fertilization of these eggs they were

*Performed at Woods Hole, Massachusetts, by Francis R. and Alice S. Hunter.

placed in salt water with various concentrations of "burn toxin" (0.5 to 3.5 mg. per milliliter). Compared to controls there was a delay of cleavage and in the higher concentrations of toxin, blastulae failed to form, indicating toxicity.

Pharmacologic Materials.—When adenosine or adenosine-5-phosphate (2 mg. per milliliter), plus the salt mixture as mentioned previously, was injected intracerebrally, one of 5 animals was killed (2 animals had questionable injections). Inosine or inosine monophosphate or adenosine triphosphate (sodium salt) in concentrations of 20 mg. per milliliter had no effect when 0.03 ml. was injected intracerebrally in 20 Gm. mice. Similarly, 40 mg. per milliliter of inosine intravenously or 20 mg. per milliliter intraperitoneally (0.1 and 0.5 ml. amounts, respectively) produced no effect in mice. Twenty milligrams per milliliter of inosine intracerebrally (0.03 ml.), however, did cause the mice to become prostrate but they lived. In the 40 mg. per milliliter dose all had severe reactions, but not exactly typical as found with the "burn toxin," and 1 of 3 mice died.

Bradykinin in 20 mg. per milliliter concentration injected (0.03 ml.) intracerebrally produced no reaction. Histamine (200 mcg. of free base per milliliter as diphosphate) when injected intracerebrally (0.03 ml. amounts) produced no reactions in these animals. Bacterial pyrogen (Pyrexal 0.5 mcg. per milliliter) in 0.03 ml. amounts produced two reactions in 5 mice, but they all lived.

Under the conditions of these experiments the salt and pharmacologically active material in the burn diffusates are not the basic cause of the lethal effects.

EXTRACTION OF "BURN TOXIN" IN VITRO

This study was undertaken expressly to rule out the effect of the muscle which is adherent to the skin of the rat and which may contribute to the "burn toxin." Air pockets were made under the skin of rats as described above and the skin was burned at 96° C. for 30 seconds. Immediately after burning the animals were killed and exsanguinated, the skin was removed immediately and frozen on dry ice, and the muscle and fat on the undersurface were trimmed off as carefully as possible. The skins were then ground in mortar and pestle with dry ice and suspended in approximately three times to eight of water to skin by weight (triple-distilled water) and placed in a refrigerator for 10 minutes with occasional stirring. The suspension was then centrifuged and resuspended in cold distilled water and again held for 10 minutes in the refrigerator. This process was repeated three times. The washes were pooled, frozen, and lyophilized. This crude extract was made up into concentration of 100 mg. per milliliter in distilled water, incubated 30 minutes at 37° C., and centrifuged, and the soluble portion injected intravenously in mice. The soluble portion of 15 mg. of crude material (0.15 ml. of 100 mg. per milliliter) killed 5 of 6 mice weighing 20 Gm. The microscopic sections taken of this skin revealed that no muscle fibers were noted, but this does not mean that there were not a few present since serial sections were not taken. One cannot compare the skin extract and burn diffusate by weight since nondiffusible material was included

in the skin extracts. Approximately two times the weight of soluble material of the skin extract as compared to the burn diffusate was lethal to mice injected intravenously.

ASHING EXPERIMENTS

On the average the crude "burn toxin" contains 40 per cent ash. Corresponding weights of the ash material and the nonash material were injected by the subcutaneous and intravenous routes. The pH of the resultant ash was approximately 11.5. This fact, plus the fact that some toxic metal oxides may be formed in the ashing, may contribute to the toxicity of the ash which was not present before the ashing occurred. Nevertheless, when equivalent amounts of ashed material as lethal nonash material were injected subcutaneously, only 2 of the 5 mice died. The type of death was atypical when compared to that produced by the crude toxin itself. Crude diffusates when injected intravenously at the level of 9 mg. (0.25 ml. of a 36 mg. per milliliter suspension) were lethal to mice. The corresponding ash was not lethal. Fifteen milligrams of a salt mixture intravenously is not lethal to 20 Gm. mice. It is of interest that when 0.2 ml. of a 0.1 normal sodium hydroxide solution (pH 12.6) was injected intravenously in mice, no reaction occurred.

DISCUSSION

The evidence presented indicates the existence of a "burn toxin" originating in the skin proper which is exclusive of histamine, bradykinin, adenyl compounds, salts, and so forth, although all may be contributing to the toxic and lethal effects inflicted upon the host. The chemical composition of this toxin or toxins is unknown. It is dialyzable, heat stable, and partially precipitated by 80 per cent ethanol. The toxin contains, among other substances, peptides, polynucleotides, and sugars. The toxin in question originates from the skin proper since the diffusates were collected from the skin circumventing the circulation. It is lethal to rats and mice. The toxic and lethal effects may be elicited when the diffusates are injected subcutaneously, intraperitoneally, intravenously, or intracerebrally. The symptoms may be acute or chronic depending upon the route of administration and the dose administered.

The contribution of heated blood within the vessels of the skin to the "burn toxin," as suggested by the work of Simonart[20] and Godfraind,[7] cannot be great. In the air pocket preparation here reported, only the capillaries of the skin are heated, and it is doubtful that sufficient blood is present to play a role in the production of the "burn toxin." It will be shown in a subsequent paper using Evans blue as an indicator that the circulation of the skin burned at 96° C. for 15 seconds is quickly arrested. On the other hand, "burn toxin" is obtained from the pockets for hours. Paper chromatography of the crude diffusate demonstrated only faint traces of blood proteins. Immunologic studies failed to demonstrate blood proteins in the toxin.

The contribution that muscle breakdown products may make in the formation of the "burn toxin," as suggested by Green and Stoner,[8] would appear

to be minimal in the preparation here described. It is understandable that in third degree burns muscle breakdown may play a prominent role. In the preparation here described, the skin overlying the air pocket in the rat does contain a very thin layer of skeletal muscle and this may account for the presence of the adenyl compounds reported after burning. However, experiments here reported show that whereas adenyl compounds may be contributory, they are not synonymous with the "burn toxin." Manyfold the amounts of adenosine, adenosine-5-phosphate, inosinic acid, inosinic mono- and diphosphate, adenosine mono- and triphosphate present in a lethal dose of the "burn toxin" are not lethal to the mouse. Finally, extracts of burned skin from which the muscle has been removed are lethal to the mouse.

Whether or not this toxin enters the circulation after it is once released is crucial to the hypothesis of a "burn toxin." It will be shown in another publication by an immunologic approach using precipitins, hemoagglutinins, and hemolysins that products of the burn diffusate do enter the circulation of burned rats. In one experiment it was demonstrated that the higher the antigenic content of diffusate, the greater the toxicity. In the normal intact animal the amount of tissue breakdown elements which enter into the general circulation is at a minimum since tissue damage is relatively low under normal conditions. In the injured animal with tissue destruction, the possibility of such substances getting into the circulation is greatly enhanced. Thus "controls" are not critical to this experiment. The so-called "controls" used in this experiment present actually another form of injury which is that due to the contact of normal tissue with hypotonic solutions such as triple-distilled water. Water was used instead of physiologic salt solutions in order to reduce the high concentrations of salts after freeze drying. Even under these conditions the crude burn diffusate contained about 40 per cent ash which is either in the form of salts or inorganic material. Whereas with devitalized tissue as occurred following a 96° C. burn, the use of water did not seem to affect the diffusion of protein products or histamine as compared to when salt solutions were used; when water was used to diffuse the pockets of normal animals, the amount of protein and histamine yield was greatly increased over that which was found when Tyrode's solution was used. This type of injury, for example, the hypotonic solution plus the manipulation, also produced a toxic substance, but the amount in milligrams of dry diffusate was only a fraction of that produced in the burned animal. The total amount of protein, nonprotein nitrogen, and salts was similar in many respects. In another publication it will be shown that antigenically these toxins differ.

The high concentration of salts in the "burn toxin" makes exclusion of this factor a difficult one. It was shown that from five to ten times the concentration of sodium, calcium, potassium, copper, and phosphorus found in a lethal dose of toxin failed to kill mice whether the salts were administered individually or in combinations and injected subcutaneously, intravenously, or intracerebrally. The fact that the crude "burn toxin" delays cleavage and inhibits blastulae formation of arbacia eggs that normally exist in salt water is additional evidence

that toxicity and salt concentration are independent. Chaet[2] found that the coelomic fluid of scalded worms (phoscolosoma goulde) inhibited division of arbacia eggs.

Ashing experiments are not entirely satisfactory to exclude salts since following ashing the formation of metal oxides might render a substance toxic that was not so before. Considering crude diffusates only, administered subcutaneously or intravenously, there was a drop of 72 and 100 per cent in toxicity, respectively, of the toxin after ashing.

Tissue damage by any means (chemical, physical, or biologic) may be associated with the liberation of split products[13, 16, 19] or denaturation of proteins, fats, and sugars which contribute to the toxic manifestations in the host. Preliminary immunologic studies indicate that some of the products following various types of tissue damage (radiation and thermal) are related but not identical.[18, 19]

SUMMARY

1. Diffusates obtained directly from the burned skin of rats circumventing the circulation are lethal to mice and rats.

2. This substance is lethal when given subcutaneously, intravenously, intraperitoneally, or intracerebrally.

3. Death may occur acutely, subacutely, or chronically depending upon the dose and the route of administration.

4. The toxic factor or factors is dialyzable, heat stable, and only partially precipitated by 80 per cent ethanol.

5. Preliminary chemical analyses of this toxic material indicate that it contains peptides, polynucleotides, hexoses, and pentoses.

6. Histamine, bradykinin, adenyl compounds, and salts may be contributory but they are not synonymous with the "burn toxin" under consideration.

REFERENCES

1. Boer, Karl A.: Pathology and Physiology of Burns (1942-1951), U. S. Armed Forces Medical Library Reference Division, Washington, D. C., June, 1952.
2. Chaet, A. B.: Demonstration of a Toxic Factor (s) in Thermal Death, Proc. Soc. Exper. Biol. & Med. **91**: 599, 1956.
3. Clark, C. P., and Collip, J. B.: A Study of the Method for Determination of Blood Serum Calcium With a Suggestive Modification, J. Biol. Chem. **63**: 461, 1925.
4. Davis, J. H., and Abbott, W. E.: The Pathology of Thermal Burns—Changing Concepts, Ann. Surg. **40**: 788, 1956.
5. Fiske, C. H., and Subarow, Y.: The Colorimetric Determination of Phosphorus, J. Biol. Chem. **66**: 375, 1925.
6. Gilmore, J. P., and Fozzard, H. A.: Hepatic Function Following Thermal Injury, Fed. Proc. **17**: 53, 1958.
7. Godfraind, T.: Toxicité des protéines chauffées et de leurs hydrolysats, Arch. internat. pharmacodyn. **105**: 412, 1956.
8. Green N. H., and Stoner, H. B.: Biological Actions of the Adenine Nucleotides, London, 1950, H. K. Lewis & Co.
9. Harkins, N. H. The Treatment of Burns, Springfield, Ill., 1942, Charles C Thomas.
10. Hunter, F. R., Rosenthal, Sol Roy, Hunter, Alice S., Finamore, F. J., and Roman, Inza-Nell: Pathogenesis of Death Due to Burns. Materials Released From the Burned Skin of Rats, Fed. Proc. **14**: 77, 1955.
11. Lasker, Sigmund E., and Fox, Charles L., Jr.: Effect of Various Types of Fluid Therapy on Survival of Monkeys Exposed to Standardized Flash Burn, Fed. Proc. **17**: 92, 1958.

12. Rocha e Silva, M., and Rosenthal, Sol Roy: Release of Pharmacologically Active substances From the Rat Skin In Vivo Following Thermal Injury. To be published.
13. Rosenthal, Sol Roy: The Toxin of Burns, Ann. Surg. **106**: 111, 1937.
14. Rosenthal, Sol Roy, Finamore, Frank J., Hunter, F. R., and Williams, Albert D.: "Toxic Factors" in Burns, Fed. Proc. **15**: 156, 1956.
15. Rosenthal, Sol Roy, Hunter, F. R., Hunter, Alice S., Finamore, F. J., Williams, Florence, and Roman, Inza-Nell: Pathogenesis of Death Due to Burns. Role of Skin, Fed. Proc. **14**: 124, 1955.
16. Rosenthal, Sol Roy, and Minard, D.: Experiments on Histamine as the Chemical Mediator for Cutaneous Pain, J. Exper. Med. **70**: 415, 1939.
17. Rosenthal, Sol Roy, Samet, Charles, Winzler, Richard J., and Shkolnik Selwyn: Substances Released From the Skin Following Thermal Injury. I. Histamine and Proteins, J. Clin. Invest. **36**: 38, 1957.
18. Rosenthal, Sol Roy, Spurrier, Wilma A., and Trahan, H.: Specificity of Thermal and Radiation (Beta) "Toxins" of the Skin, Fed. Proc. **17**: 135, 1958.
19. Rosenthal, Sol Roy, and Trahan, Harold: "Burn Toxin"; Absorption From Burn Site, Fed. Proc. **16**: 370, 1957.
20. Simonart, A.M.: Au sujet de l'auto-intoxication aprés brulure, Bull. Acad. roy. med. (Belgique) **20**: 75, 1955.
21. Sørensen, M., and Haugaard, C.: Über die Ansendbarkeit der Orcinreaktion zur Bestimmung der Art und Menge von Kohlenhydrat Gruppen in Eiweisstoffen. Biochem. Ztschr. **260**: 247, 1933.
22. Symposium on Burns (Nov. 2-4, 1950), National Research Council Committee on Surgery: Subcommittee on Burns, Washington, D. C., 1951.

EFFECT OF CYCLOPROPANE ANESTHESIA ON BLOOD COAGULATION

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IN 1937, 4 years after the introduction of cyclopropane as an anesthetic agent, Marshall[7] mentioned that excessive bleeding occurred during its administration. Subsequently, McLoughlin[6] found that the blood loss following a standard needle puncture was inversely proportional to the depth of cyclopropane anesthesia in planes 1 and 2. In the deeper planes (3 and 4) blood loss was greater when respiratory acidosis developed. Comparison of mean blood loss in plane 2 of cyclopropane and ether anesthesia showed that at this depth, cyclopropane produced approximately one and one half times as much bleeding as ether.

Although it is generally accepted that bleeding is greater with cyclopropane than with other anesthetics, there has been no thorough investigation of the clotting mechanism during cyclopropane anesthesia.

METHODS

Fifteen patients undergoing unselected surgical procedures were anesthetized to the second plane of cyclopropane anesthesia (judged both by electroencephalographic changes and clinical signs) for 50 to 120 minutes. Blood samples for clotting studies were withdrawn by atraumatic venipuncture prior to anesthesia, during second plane cyclopropane anesthesia, and postoperatively.

In a second group of 6 patients, hypercarbia was produced during plane 2 cyclopropane anesthesia by rebreathing for 15 minutes with resultant CO_2 tensions of 57 to 62 mm. Hg. Blood samples for clotting studies, pH, and P_{CO_2} were taken preanesthesia, during second plane cyclopropane anesthesia, after 15 minutes of rebreathing, and postoperatively. None of the patients in either series received blood transfusions.

The following tests were carried out on most patients: prothrombin time (3), content of prothrombin, factor V, and factor VII plus Stuart factor (3), prothrombin consumption (3), thromboplastin generation test (using 25 mg. per cent cephalin* instead of platelets, and $BaSO_4$ adsorbed oxalated plasma) (4), plasma thrombin clotting time (3), fibrinogen concentration (5), spontaneous fibrinolytic activity of the euglobulin fraction (6), whole blood clot lysis, and antiplasmin activity (6). In about half of the patients the following tests

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*Inosithin from soy beans, Associated Concentrates, Woodside, N. Y.

were also performed: tourniquet test (100 mm. Hg for 4 or 5 minutes) bleeding time (40 mm. Hg cuff pressure, fingertip puncture), platelet count (7), clotting time in glass, clotting time in silicone, and observation of clot retraction.

RESULTS

Control values were within the normal range in all patients. During anesthesia, only three factors showed significant deviations from control values. These were an increased platelet count in 3 cases and a decrease in 2 cases; a decreased factor V content in 3 cases; and fibrinolysis at some time in 5 of the 21 patients (Table I).

TABLE I. NUMBER OF PATIENTS SHOWING CHANGES IN CLOTTING FACTORS WITH CYCLOPROPANE

	C_3H_6	$C_3H_6 + CO_2$
Number of patients	15	6
No change	13	3
Fibrinolysis	2	3
Preanesthesia only	1	0
Preanesthesia, during, and postoperatively	0	2
During operation	1	1
Factor V decrease	1	2
Platelet count decrease	2	0
Platelet count increase	1	2
Clinical evidence of increased bleeding	0	0

Although there were changes in the platelet count of as much as 200,000 per cubic millimeter, no counts were below 160,000 or above 500,000 per cubic millimeter, which are the limits of the normal range. The factor V depression was not marked, the lowest value being 57 per cent (lower limit of normal about 70 per cent). Fibrinolytic activity of the euglobulin fraction with lysis in less than 10 hours occurred preanesthesia in 3 of the 5 positive cases. In one of these patients it occurred preanesthesia only, and in 2 patients in whom hypercarbia was produced it occurred preanesthesia, during, and after the operation. Fibrinolytic activity was present during operation alone in one of the 15 patients receiving cyclopropane and in one of the 6 patients receiving cyclopropane with hypercarbia. None of the patients had whole clot lysis.

In none of the 21 patients was there clinical evidence of increased bleeding or oozing as judged by the surgeon.

DISCUSSION

The increased bleeding which has been reported during cyclopropane anesthesia is apparently real, although the evidence in support of this belief is meager. McLoughlin's report[6] that there was one and one half times as much bleeding with cyclopropane as with ether anesthesia is the only well-documented study.

The increased bleeding that occurred during cyclopropane anesthesia might be due to many factors. Some of these are the effect of chemical changes (such as the anesthetic itself), anoxia, or carbon dioxide upon either the clotting mechanism or the circulation producing, for example, vasodilatation, venous congestion, or elevated venous pressure.

An interpretation of the tests of blood coagulation requires an understanding of the various factors concerned with the formation and maintenance of the blood clot.

The process of blood clotting has been divided into three stages: (1) the formation of thromboplastin, (2) the formation of thrombin from prothrombin, and (3) the conversion from fibrinogen to fibrin. Recent evidence[8] indicates that a more precise description is provided by considering two types of conversion of prothrombin to thrombin: (1) by the intrinsic system (no added source of tissue thromboplastin) and (2) by the extrinsic system (after addition of tissue thromboplastin) (Fig. 1). The intrinsic system leads to the production of so-called plasma thromboplastin and the necessary factors are present in blood in either active or precursor forms. Deficiency is indicated by prolonged clotting time, poor prothrombin consumption, and abnormal thromboplastin generation tests, as well as specific assays. The tests used to determine platelet abnormalities are the platelet count, special tests for platelet clotting factors, clot retraction, bleeding time, and perhaps tourniquet test. Deficiencies of factors required for the extrinsic system are most readily detected by prolonged prothrombin time.

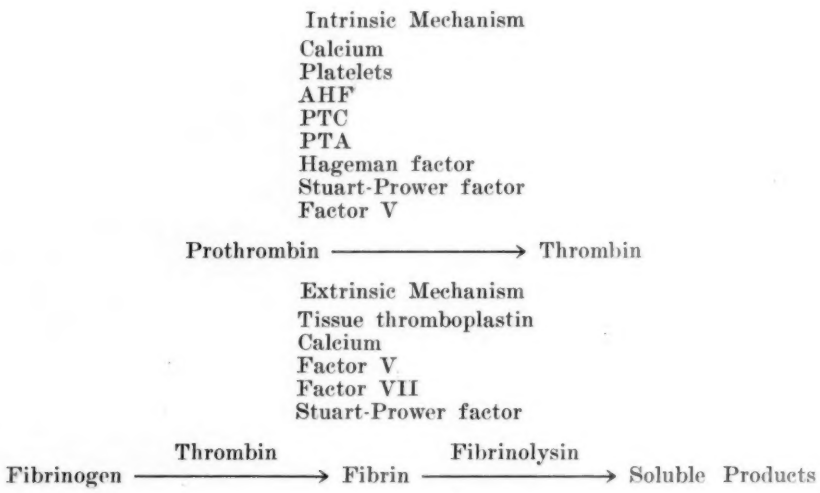

Fig. 1.

The final stage of clotting is the formation of the fibrin clot and depends upon the presence of thrombin and fibrinogen. Defects in this stage may be found by determining the thrombin clotting time and fibrinogen concentration.

The presence of an abnormal degree of fibrinolysis is revealed by fibrinolytic activity of the plasma euglobulin fraction and by whole blood clot lysis. Additional insight into this process is provided by measuring antiplasmin activity.

Our results failed to demonstrate any common or consistent change in clotting factors in patients anesthetized with cyclopropane who did not show excessive bleeding. Factor V fell significantly in 3 patients. The decrease may

have resulted from destruction by fibrinolysin[11] since all 3 patients had fibrinolytic activity prior to or at the same time as the low factor V. Although euglobulin lysis times were as short as 2 hours in 2 patients, whole blood clot lysis did not occur. Factor V changes were not marked; the lowest value (57 per cent) was only slightly below the lower limit of normal (70 per cent). It is not surprising that the patients did not exhibit excessive bleeding. In our experience,[12] operative bleeding is usually associated with multiple abnormalities of the clotting mechanism.

In a previous study with di-ethyl ether as the primary agent,[12] a similar analysis was carried out on 30 patients. Fibrinolysis occurred preanesthesia in 3 patients and during anesthesia in 10 patients. In none of these patients was clinical evidence of oozing noted. Thus, there was no difference in the occurrence of fibrinolysis with the two anesthetic agents.

When increased bleeding does occur during cyclopropane anesthesia, there is suggestive evidence that fibrinolysis might be responsible. It has been our clinical experience that patients who exhibited increased bleeding during cyclopropane anesthesia had a wound which oozed dark thick blood. This type of ooze is also seen when fibrinolysis is occurring. Biggs and his associates[2] have shown that exogenous adrenaline as well as anxiety produce fibrinolysis. Cyclopropane increases the concentration of circulating norepinephrine, and cyclopropane combined with hypercarbia increases both epinephrine and norepinephrine concentrations.[9] Our results suggest that hypercarbia may perpetuate fibrinolysis. Fibrinolysis which was present before the administration of anesthesia did not persist throughout the operation in one patient who received cyclopropane alone, but fibrinolysis did persist into the postoperative phase in the 2 patients in whom cyclopropane and hypercarbia were both present.

SUMMARY

An analysis was made of blood clotting changes in 15 patients receiving cyclopropane and in 6 patients receiving cyclopropane with induced hypercarbia. No evidence of clinical oozing occurred and there was no apparent difference in the changes in blood clotting factors from those observed with ether anesthesia.

We wish to express our appreciation to Mavis Clarke for her competent technical assistance.

REFERENCES

1. Biggs, R., and Douglas, A. S.: The Thromboplastin Generation Test, J. Clin. Path. **6**: 23-29, 1953.
2. Biggs, R., MacFarlane, R. G., and Pilling, J.: Observations on Fibrinolysis, Lancet **1**: 402-405, 1947.
3. Brecher, G., Schneiderman, M., and Cronkite, E. P.: The Reproducibility and Constancy of the Platelet Count, Am. J. Clin. Path. **23**: 15-26, 1953.
4. Cliffton, E. E., and Cannamela, D. A.: Proteolytic and Fibrinolytic Activity of Serum, Blood **8**: 554-562, 1953.
5. Lewis, J. H., Ferguson, J. H., Fresh, J. W., and Zucker, M. B.: Primary Hemorrhagic Diseases, J. Lab. & Clin. Med. **49**: 211-232, 1957.
6. McLoughlin, G.: Bleeding From Cut Skin and Subcutaneous Tissue Surfaces During Cyclopropane Anesthesia, Brit. J. Anaesth. **26**: 84-99, 1956.
7. Marshall, S. U.: Cyclopropane Anesthesia: A Preliminary Survey, M. J. Australia **2**: 138-141, 1937.

8. Owren, P. A.: Coagulation of Blood, Northwest Med. **56**: 31-39, 1957.
9. Price, H. L., Lurie, A. A., Jones, R. E., Price, M. L., and Linde, H. W.: Cyclopropane Anesthesia. II. Epinephrine Nor-epinephrine in Initiation of Ventricular Arrhythmias by Carbon Dioxide Inhalation, Anesthesiology **19**, 5: 619-630, 1958.
10. Quick, A. J.: The Physiology and Pathology of Hemostasis, Philadelphia, 1951, Lea & Febiger.
11. Soulier, J. P., Alagille, D., and Larrieu, M. J.: In Vivo and In Vitro Proteolysis of Coagulation Factors Other Than Fibrinogen, International Society of Hematology, 6th Congress, Boston, 1956, New York, 1958, Grune & Stratton, Inc., p. 488.
12. Zucker, M. B., Siegel, M., Cliffton, E. E., Bellville, J. W., Howland, W. S., and Grossi, C. E.: Generalized Excessive Oozing in Patients Undergoing Major Surgery and Receiving Multiple Blood Transfusions, J. Lab. & Clin. Med. **50**: 849-861, 1957.

EXPERIMENTAL GRADUAL ARTERIAL OCCLUSIONS WITH IN VITRO AND IN VIVO OBSERVATIONS

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THE present study is concerned with the development of a method for gradually occluding arteries over predictable periods of time without risk of dangerous or undesirable side effects.

Four experiments were designed to determine the capabilities of certain promising methods of gradually occluding blood vessels. In the first experiment, dicetyl phosphate-coated cellophane was wrapped around peripheral arteries in dogs and observations were made to determine the extent of arterial occlusion produced. The second experiment was concerned with quantitating the rate of swelling of casein plastic material in vitro. These results directed the choice of casein plastic sleeve designs to be used on peripheral and coronary arteries in the third and fourth experiments.

PART I. THE PROPERTIES AND EXPERIMENTAL APPLICATIONS OF CELLOPHANE AND DICETYL PHOSPHATE IN THE GRADUAL OCCLUSION OF ARTERIES

Reports on the use of cellophane discussed its inert qualities[5, 12, 17] while other authors reported marked tissue reactions to cellophane in the body.[14, 15] Many investigators have used cellulose cellophane to produce fibrosis around blood vessels in order to effect occlusion.[4, 7, 15]

When polyethylene film began to replace cellulose cellophane commercially, this material was also used as a wrapping to occlude blood vessels. While some authors reported fibrosis around vessels as a result of polyethylene wrapping,[1, 3, 18] other investigators discussed its biologic inertness.[9] Later, a contaminant (dicetyl phosphate) was recovered from polyethylene film, which was found to be the factor producing fibrosis.[18]

Because the combined use of cellulose cellophane and dicetyl phosphate had not been reported nor their combined action in occluding blood vessels quantitated, the first experiment was developed.

Materials and Methods.—Du Pont PT-450 cellophane was cut into strips, immersed in a toluene solution of dicetyl phosphate, then dried. Widths of 2, 4, 6, and 8 cm. were folded in half, wound twice around each vessel, and held loosely in place with cotton ligatures.

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Twelve mongrel dogs were used. Under aseptic conditions, strips 4 cm. in width were applied to right carotid and left femoral arteries, and 3 cm. widths to right femoral arteries. Strips 2 cm. wide were wrapped around left carotid and left brachial arteries, and 1 cm. widths were applied to right brachial arteries.

The vessels were re-explored at various intervals 2 to 60 days after wrapping for the following three tests of occlusion: (1) palpation for arterial pulsations proximal and distal to the cellophane wrapping and (2) transection of the arteries distal to the cellophane wrapping to observe blood flow through the wrapped segment. (3) The cellophane wrapped arterial segments were removed and attached to an apparatus (Fig. 1) which produced a constant saline flow. Any reduction in control flow would, therefore, result from narrowing of the vascular lumen. Each arterial segment was removed from the wrapping and studied histologically.

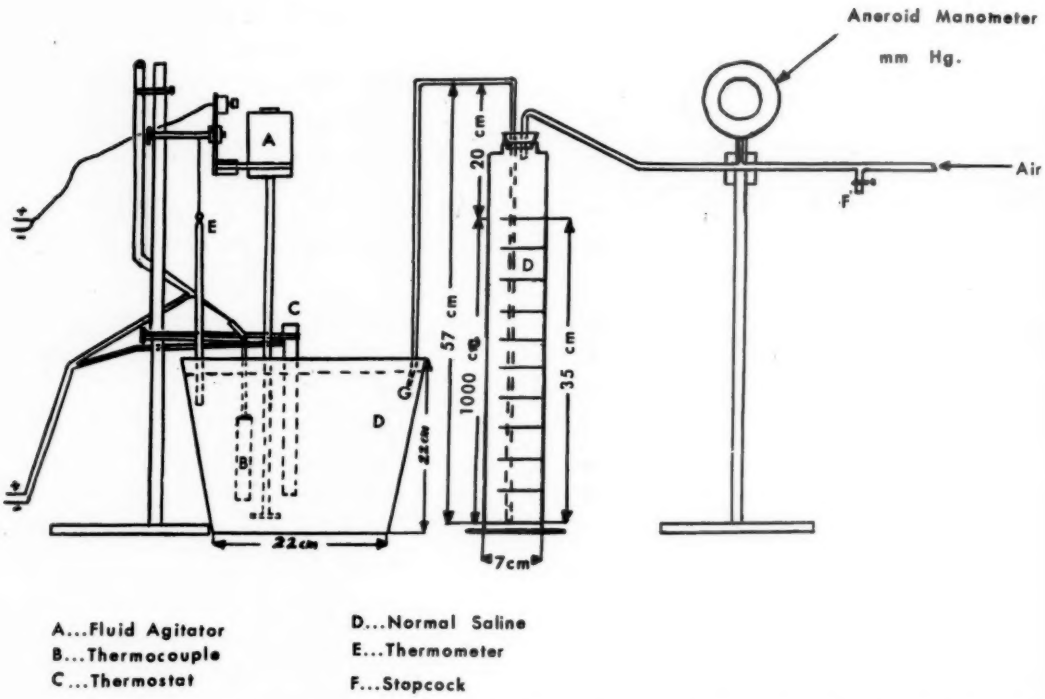


Fig. 1.—Saline water bath with agitator and aneroid-saline pressure flow apparatus. Apparatus was used to determine rate of flow through excised arterial segments. Petcock *F* was adjusted so that the aneroid manometer registered 100 mm. Hg pressure with graduate *D* filled with saline and tubing end *G* clamped. The saline bath, agitator, thermocouple, and thermostat (*A, B, C, D*) were used to maintain the arterial segment (or heart) at 44° C. Control flow through the apparatus was 280 c.c. per minute. Tubing end *G* was inserted into the artery segment to be tested.

Results.—In the tests of vascular occlusion, it was noted that pulsation of the arteries persisted proximal and distal to the cellophane strip in every wrapped vessel. Every vessel bled freely when the arteries were transected distal to the cellophane wrapping. None of the wrapped arterial segments diminished the flow of normal saline from a constant output of 280 c.c. per minute (Fig. 1).

Histologic examinations of artery segments 2, 5, 10 and 15 days after wrapping showed inflammation of the adventitia which was interspersed with particles of grayish pearly white amorphorus material (dicetyl phosphate). After 20, 30, and 60 days, the changes in the adventitia were more granulomatous. There were no significant changes in the tunica intima or media of any vessels.

Discussion.—Regardless of duration of application or width of these cellophane strips soaked in dicetyl phosphate, there was no significant occlusion of any arteries in this series.

PART II. ARTERIAL OCCLUSION BY MEANS OF EXTERNAL COMPRESSING DEVICES AND PRELIMINARY EXPERIMENTAL CONSIDERATIONS OF CASEIN PLASTIC MATERIAL

In view of the unsatisfactory results obtained with cellophane and dicetyl phosphate in producing gradual occlusion of arteries, other methods were sought.

External compression of arteries by means of loops, rings, screws, clamps, and other surgical materials has been attempted experimentally and clinically over the past 100 years. Most of these have been discarded, while others are still being evaluated.[4, 6, 8, 13, 15]

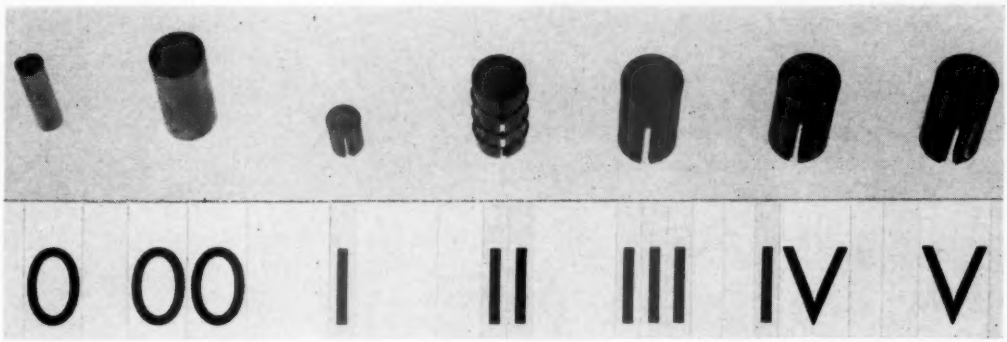


Fig. 2.—Photograph of casein plastic stock rods (0 and 00) and fabricated sleeves (I, II, III, IV, V). *Types 0 and 00* were 12 mm. lengths of 6 and 12 mm. diameter casein plastic stock as supplied from the factory. *Type I sleeve* was made of 6 mm. diameter stock plastic with a 3 mm. diameter lumen and encased in stainless steel, 1 mm. in thickness. It was made in 5 and 10 mm. lengths. *Type II sleeve* was made of 12 mm. diameter stock plastic with an eccentrically placed 5 mm. diameter lumen and wound with three separate wires. *Types III, IV, and V sleeves* were made of 12 mm. diameter stock plastic with 5, 6, and 7 mm. diameter lumens, respectively. They were encased in stainless steel, 1 mm. in thickness, and were made in 8 and 25 mm. lengths.

The use of the hygroscopic properties of compressed casein plastic in producing gradual arterial occlusion has been promising. Berman reported that casein plastic cylinders swelled when immersed in saline and, in the form of specially designed sleeves, were capable of occluding arteries.[1, 2]

Casein plastic is manufactured by mixing powered Rennet casein with water. Rods of varying dimension are formed by extrusion under increased pressure and temperature. The rods are hardened for a prolonged period in formalin.[16]

Materials and Methods, In Vitro Experiment.—Casein plastic rods were supplied from the factory in 6 and 12 mm. diameters, about 50 cm. in length.* Pieces of stock plastic rods and sleeves of many designs were fabricated (Fig. 2) and the rate and amount of swelling were determined by measurement of

*American Plastics Corporation, Bainbridge, New York.

internal or external diameters after various periods of immersion in normal saline at 38° C. Certain sleeves were encased in stainless steel, 1 mm. in thickness, and a longitudinal slot was cut along the side of the casein and plastic sleeve to allow the vessel to be inserted into the sleeve. All test forms were maintained within a dehydrating desiccator prior to use to produce uniformly equal initial diameters.

Type numbers 0, 00, I, II, III, IV, and V were assigned to the various test forms (Fig. 2) for purposes of identification.

Types 0 and 00 (Fig. 2) were 12 mm. lengths of stock casein plastic bar, 6 and 12 mm. in diameter, respectively, without a casing or lumen. These types were observed for gross rate of external swelling.

The type I sleeve (Fig. 2) was made of 6 mm. diameter casein plastic bar encased in stainless steel with a 3 mm. diameter lumen. Five and 10 mm. lengths of this sleeve were observed for rate of luminal narrowing. Glycerine and petrolatum-coated forms were also tested.*

Type II sleeves (Fig. 2)made of 12 mm. diameter plastic rod had eccentrically placed lumina of 5 mm. diameter and were wrapped with 3 evenly spaced wires. Luminal and external rates of narrowing and swelling were recorded.

Sleeves of *types III, IV, and V* (Fig. 2) were made of 12 mm. diameter stock bar and encased in stainless steel housings. They differed only in luminal diameters, which were 5, 6, and 7 mm., respectively. Twenty-five and 8 mm. lengths of these sleeves as well as glycerine and petrolatum-coated forms were observed for rate of luminal narrowing.

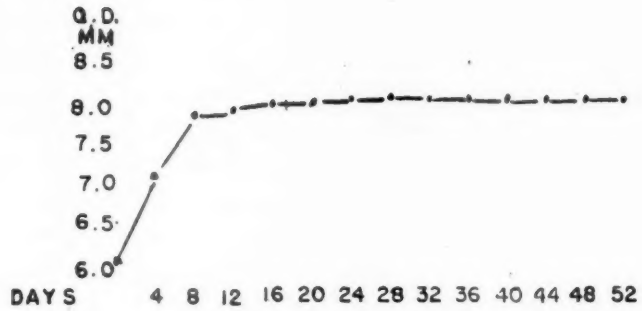
Results.—Immersion of various types of casein plastic stock bar and sleeves in normal saline at 38° C. produced swelling of the plastic, transforming it to a soft rubbery consistency. Encasement in a stainless steel sleeve directed the swelling plastic toward a previously cut lumen. The plastic shrank into rigid distorted forms when removed from saline and allowed to dry.

Types 0 and 00 casein plastic stock bars (Figs. 2 and 3): The uncoated 6 and 12 mm. diameter stock bars of casein plastic swelled rapidly in the first 2 to 3 weeks of immersion, expanding more slowly during the remainder of the test period. Therefore, a simple coefficient of expansion could not be determined.

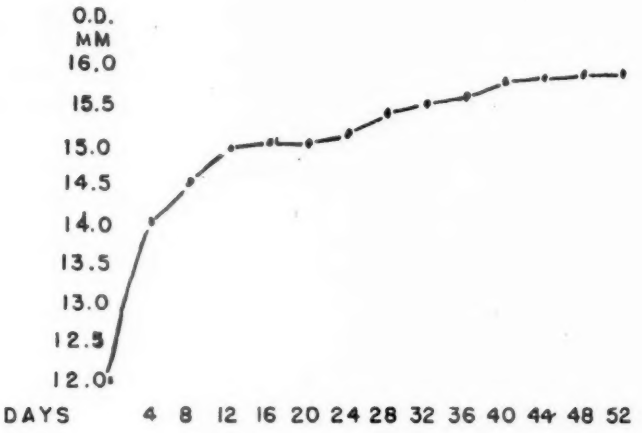
Type I casein plastic sleeves (Figs. 2 and 4): These sleeves expanded luminally at the rate given in Fig. 4. Glycerine coating of this type (*b*) made little difference in the rate of narrowing in the first 40 days compared to the uncoated sleeve. Petrolatum coating (*c*) produced an almost linear rate of narrowing to the twentieth day which lagged behind the plain and glycerine-coated sleeves. Thereafter, the luminal diameter decreased gradually, lagging behind that of the glycerine-coated sleeves.

Type II casein plastic sleeves (Fig. 2): It was proposed that the eccentricity of the lumen plus wire wrapping would result in narrowing of the lumen without having to resort to a rigid housing. Measurements of this sleeve were not considered valid, because the rubbery soft plastic yielded to the passage of

*These sleeves were immersed in glycerine or liquified petrolatum in a water bath for one full hour immediately prior to use.



A.



B.

Fig. 3.—Graph depicting rate of external diameter swelling of stock type 0 6 (*A*) and type 00 12 mm. (*B*) diameter casein plastic in normal saline. (See Fig. 2 for illustration and dimensions.)

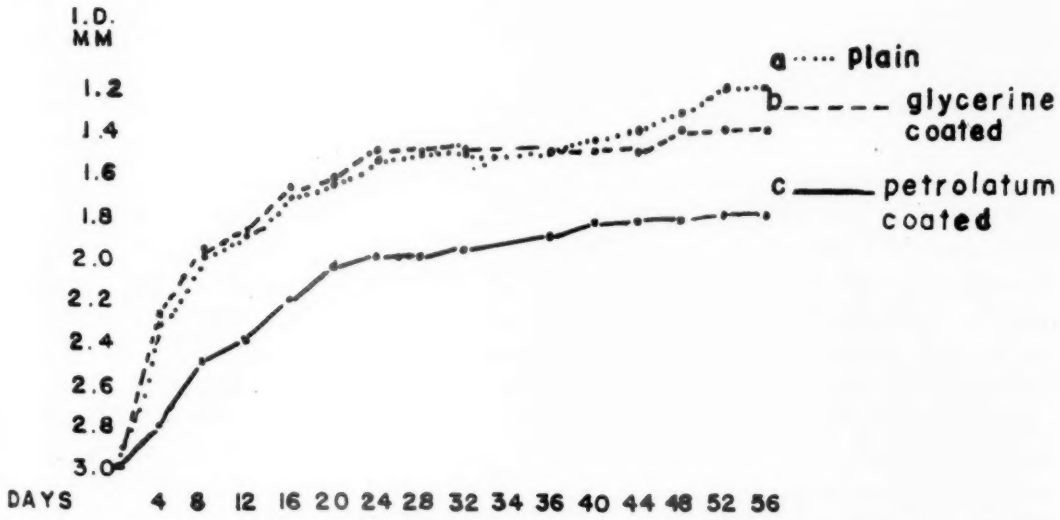


Fig. 4.—Graph depicting the rate of luminal narrowing of coated and uncoated type I casein plastic sleeves in normal saline. (See Fig. 2 for illustration and dimensions.)

widely varying sized external and internal circumferential calipers. Neither the wrapping wires nor the eccentricity of the lumen was very effective in directing the swelling plastic luminally.

Types III, IV, and V casein plastic sleeves (Figs. 2 and 5): An example of rate and amount of luminal narrowing of type III, IV, and V sleeves is given in Fig. 5, using the type V sleeve as being typical for coated and uncoated forms. Glycerine (*a*) and petrolatum (*b*) coating of these sleeves produced little alteration in the rate of luminal narrowing over the first week of immersion in saline. Thereafter, the luminal diameters decreased more slowly for glycerine-coated sleeves, and even more slowly for those coated with petrolatum.

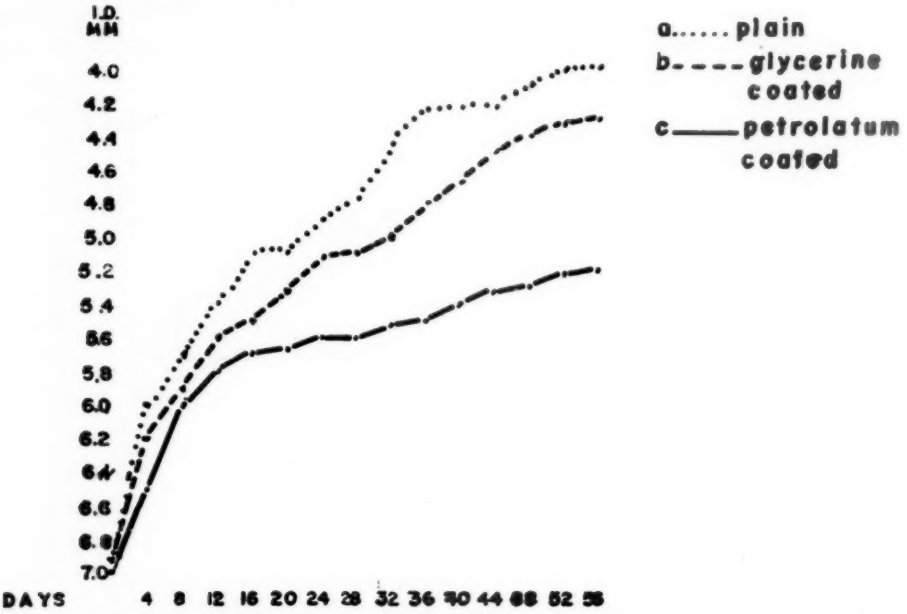


Fig. 5.—Graph depicting the rate of luminal narrowing of coated and uncoated type V casein plastic sleeves in normal saline. The pattern of swelling was typical for types III, IV, and V, which varied only in original luminal diameters of 5, 6, and 7 mm., respectively. (See Fig. 2 for illustrations and dimensions.)

PART III. OBSERVATIONS CONCERNING CASEIN PLASTIC SLEEVES APPLIED TO SEGMENTS OF PERIPHERAL ARTERIES

In order to test the reaction of peripheral arteries to the application of casein plastic sleeves and observe any alterations in flow, sleeves were applied to femoral and carotid arteries of 16 dogs.

Materials and Methods.—Types II, III, IV, and V sleeves (Fig. 2) were applied to left and right femoral and left and right carotid arteries respectively in 12 dogs. All of these sleeves were 25 mm. long and made of 12 mm. diameter casein plastic stock bar. Types II and III sleeves had 5 mm. diameter lumina, with the type III sleeve encased in stainless steel. Types IV and V sleeves were both encased in stainless steel and had luminal diameters of 6 and 7 mm. respectively. The sleeve-encased arteries in this group were re-explored at various intervals 8 to 120 days after sleeve application.

In 4 dogs, types II, III, IV, and V sleeves (Fig. 2) of 8 mm. length were applied to the same arteries, respectively, as in the foregoing group of 12 dogs.

These dogs were studied at 7, 14, 21, and 28 days, respectively, after sleeve application.

The sleeves were stored in a dehydrating desiccator prior to use to maintain uniform diameters. They were sterilized in 1:1000 Zephiran solution and applied to the arteries under aseptic conditions.

The sleeve-encased arteries were exposed for the following tests of occlusion at a given time: (1) palpation for arterial pulsations proximal and distal to the sleeve site; (2) transection of arteries distal to the sleeve to observe whether or not blood would pass through the sleeved segment, and (3) removal of sleeved arterial segments for tests of in vitro flow of saline through them at a constant pressure (Fig. 1) Each arterial segment was removed from the sleeve and studied histologically. Final luminal diameters of sleeves were then measured.

Diodrast was injected into the right femoral artery of one dog on which a casein plastic sleeve had been applied for 29 days.

Results.—Casein plastic sleeves not encased in stainless steel (type II) produced massive inflammation and necrosis resulting in erosion of the sleeve through the skin within 3 weeks of application. Exploration of the site revealed that the artery had been transected, but there was no evidence of hemorrhage.

Sleeves 25 mm. long encased in stainless steel consistently produced gradual narrowing of arteries over periods of time which varied with the luminal diameter of the sleeve. Arterial pulsations were absent by the twenty-seventh day with 5 mm. luminal diameter sleeves and by the thirty-sixth day with the 6 and 7 mm. luminal diameter sleeves. Blood flow from the transected distal end of all these arteries was significantly reduced by the thirty-sixth day of sleeve application. In vitro saline flow (Fig. 1) through arteries encased in sleeves with a 5 mm. luminal diameter was arrested by the thirty-sixth day and, in the case of sleeves of 6 and 7 mm. luminal diameter, by the one hundred twentieth day of sleeve application.

In the group of 4 dogs with 8 mm. length sleeves, palpation of arterial pulsations was difficult by the twenty-eighth day as opposed to the thirty-sixth day in the 25 mm. length sleeves. Arterial blood flow distal to the sleeved segment was diminished by the twenty-first day in the 5 mm. luminal diameter sleeve and the twenty-eighth day in the 6 mm. luminal diameter sleeve. This may be compared to the twenty-ninth and thirty-sixth days in the 25 mm. length sleeves with similar lumina. Saline flows through these arterial segments diminished directly with time, and the final luminal diameters of these sleeves were essentially the same as their 25 mm. length counterparts. The final luminal diameters of all sleeves compared almost exactly with the average measurements obtained in the in vitro study (part II).

Results of the Diodrast injection are pictured in Fig. 6, revealing a functional occlusion to the passage of the dye and presence of collateral circulation.

Microscopic observations of sleeve-encased arterial segments were carried out from 8 to 120 days. After 8 days of sleeve application, inflammation was noted in all tunics and, rarely, there were small concentric thrombotic-like attachments to the intima. At 22 days, the adventitial tunic was thin and compressed and contained chronic inflammatory cells. The appearance of this tunic

was relatively unchanged for the remaining 120-day test period. The medial tunic became homogeneous by the twenty-second day, and elastic fibers had reverted to a collagenous appearance. Within the intima, there was a concentrically organized thrombus which blended with collagenous fibers of the media. Luminally, a fibrin meshwork was piling up, thickly invested with clotted blood products.

In all later specimens examined (up through 120 days), collagenous adventitial bands blended with coarse fibers of the media which in turn blended homogenously with the organizing luminal thrombus. The lumina were completely occluded after the thirty-sixth day in arteries encased with 25 mm. length sleeves. The external diameter of all vessels appeared smaller by degrees, varying directly with the time of sleeve application.

There was no evidence that the intravascular thrombus extended more than a centimeter proximal or distal to the area covered by the sleeve.

Fig. 6.—Roentgenogram of a Diodrast injection proximal to a casein plastic sleeve in the right femoral artery of a dog 29 days after sleeve application. There was functional occlusion to the dye within and in proximity to the sleeved segment.

PART IV. CONSIDERATION OF EFFECTS RESULTING FROM APPLICATION OF CASEIN PLASTIC SLEEVES TO CORONARY ARTERIES IN DOGS

The final fascicle of this project was designed to produce occlusion of smaller arteries which subserve a vital structure. The clinical and pathoanatomic features of this work have been presented elsewhere.[10, 11] Microscopic observations of casein plastic sleeve-encased coronary arteries have recently been completed and are presented here.

Type I sleeves (Fig. 2) of 6 mm. diameter casein plastic, encased in stainless steel and having a 3 mm. lumen, were cut to 5 mm. lengths. These sleeves were applied to major branches of the left coronary artery in 12 dogs.

All of the dogs subjected to this procedure died within 4 to 26 days after thoracotomy with evidence of progressive coronary artery occlusion and myocardial infarction. Clinical observations and serial ECG studies were made while the dogs survived, and autopsies were done after death. Various pathologic and contrast medium injection x-ray studies were obtained on the coronary vasculature.[10, 11] Sleeve-encased coronary arteries were studied histologically.

Microscopically, from the fourth to the twenty-sixth day of sleeve application, the tunica adventitia gradually became thinner, less vascular, and more coarse in appearance. It blended without abruptness into the tunica media, especially after the fifteenth day. The tunica media became thickened gradually with time, and after the sixth day of sleeve application smooth muscle fibers assumed a fibrocollagenous appearance. After 13 days, the inner elastic membrane could no longer be identified. The fibers of the tunica media blended evenly with concentric whorls of organizing luminal thrombus. A fine feltwork of fibrin continued to gather luminally.

External diameters of arteries diminished directly with the time of sleeve application. Diminution in total vessel diameter was superadded to thickening of the medial tunic and accretion of luminal thrombus.

In the 25- and 26-day specimens, only a very minute opening marked the lumen of the artery which is judged to be approximately one-eighth to one-tenth the original diameter microscopically. None of these arterial lumina were completely occluded.

Discussion.—All 12 dogs expired shortly after application of casein plastic sleeves to branches of the left coronary artery. There is substantial evidence that death resulted from gradual occlusion of coronary artery branches in view of observations consistent with disturbance of the depolarization mechanism and progressive myocardial infarction.[10, 11] The mechanism for occlusion of these arteries is essentially the same as that given for peripheral arteries. It cannot be concluded with certainty that thrombotic emboli did not originate from the sleeve sites. However, no thrombi were found in distal arterial trunks by gross observation of these transversely sectioned hearts.

SUMMARY

An experiment was devised to determine quantitatively what might be expected from dicetyl phosphate-coated cellophane wrapping in occluding arteries. Results indicate that no detectable degree of arterial occlusion was produced. These results prompted further experimentation for a more effective means of occluding arteries.

Consideration of the use of casein plastic material in the form of a sleeve was prompted by encouraging reports of its ability to occlude blood vessels.

The plain sleeve not encased in a rigid housing, wrapped with bands of wire and with eccentrically placed lumina expanded in all dimensions resulting in

negligible narrowing of the lumen. Massive inflammatory responses around these sleeves in dogs finally discouraged any further experimentation with them.

Casein plastic sleeves with centrally placed lumina and encased in stainless steel were found to narrow luminally when placed in saline solution. This type of sleeve gradually occluded segments of carotid, femoral, and coronary arteries in substantially predictable periods of time.

Microscopic and gross observations of arteries encased in sleeves revealed that occlusion probably resulted from the following mechanisms: (1) reduction in external vessel diameter due to luminal swelling of the plastic, (2) fibroblastic response of the arterial walls at the site of sleeve application, and (3) formation of intraluminal thrombi arising concentrically from the intima. If an artery was completely occluded, a narrow zone of thrombotic material filled the lumen proximal and distal to the sleeve site. There was no evidence of thrombotic embolization from sleeve sites by gross observation of transversely sectioned distal arterial branches.

The final luminal diameters of all sleeves (in vitro and in vivo) of comparable dimensions were similar over comparable periods of time. Stainless steel-encased sleeves 8 mm. long occluded arteries almost one week earlier than the time expected for 25 mm. length sleeves.

Smaller casein plastic sleeves encased in stainless steel were capable of gradually occluding branches of the left coronary artery in dogs. Clinical, serial ECG, and pathoanatomic results were indicative of progressive coronary artery insufficiency and myocardial infarction.[10, 11] Microscopically, none of the coronary artery lumina were completely occluded.

CONCLUSIONS

1. No significant amount of occlusion was produced in arteries wrapped with dicetyl phosphate-coated cellophane.

2. Casein plastic sleeves which are not encased in rigid containers expand in all dimensions by hygroscopic swelling with very little luminal narrowing. They are unsatisfactory for biologic implantation.

3. The luminal narrowing of casein plastic sleeves in stainless steel housings can be reduced to a slower rate by coating the sleeves with glycerine, and to still a slower rate by coating with petrolatum.

4. Casein plastic sleeves encased in stainless steel produce gradual occlusion of carotid, femoral, and coronary arteries over reasonably predictable periods of time.

5. Casein plastic sleeves produced gradual occlusion of arteries by a combination of: (a) mechanical narrowing of the vessel due to hygroscopic swelling of the plastic, (b) fibroblastic reaction in the arterial walls, and (c) intraluminal thrombosis within and immediately surrounding the zone of sleeve application.

6. Casein plastic sleeves have produced progressive myocardial ischemia and infarction in dogs without complete anatomic occlusion of coronary arteries.

This work was carried out under the supervision of Dr. Arthur M. Vineberg. Drs. Donald R. Webster and Theodore Rasmussen were consulted on numerous occasions contributing to the instigation and completion of this project.

REFERENCES

1. Berman, J. K., and Fields, D. C.: Advanced Atrophic Cirrhosis; Present Status of Hepatic, Splenic, and Left Gastric Arterial Occlusions as an Aid in the Control of Its Complications, A. M. A. Arch. Surg. **68**: 432-441, 1954.
2. Berman, J. K., Fields, D. C., Judy, H., Mori, V., and Parker, R. J.: Gradual Vascular Occlusion, SURGERY **39**: 399-410, 1956.
3. Berman, J. K., and Hull, J. E.: The Treatment of Aneurysms With Fibroblastic Agents; Experimental and Clinical Studies With the Use of Sodium Dicetyl Phosphate, Surg. Gynec. & Obst. **94**: 543-549, 1952.
4. Burchell, H. B.: Adjustments in Coronary Circulation After Experimental Coronary Occlusion, With Particular Reference to Vascularization of Pericardial Adhesions, Arch. Int. Med. **65**: 240-262, 1940.
5. Donati, D.: Richerche sperimentali sull'uso del cellophane in plastiche durali di varia grandezza, Bull. sc. med., Bologna **109**: 425-432, 1937.
6. Goldblatt, H.: Hypertension: Experimental, by Constriction of Main Renal Arteries; Method, M. Physics, pp. 622-625, 1944.
7. Gross, R. E.: Complete Surgical Division of Patent Ductus Arteriosus; Report of 14 Successful Cases, Surg. Gynec. & Obst. **75**: 36-43, 1944.
8. Halsted, W. S.: Partial Occlusion of the Thoracic and Abdominal Aorta by Bands of Fresh Aorta and of Fascia Lata, Tr. Am. S. A. **31**: 218, 1913.
9. Ingraham, F. D., Alexander, E., Jr., and Matson, D. D.: Medical Progress; Synthetic Plastic Materials in Surgery, New England J. Med. **236**: 362, 402, 1947.
10. Litvak, J.: Experimental Production of Gradual Vascular Occlusions, Thesis submitted in partial fulfillment of requirements for the degree of Master of Science, McGill University, Department of Neurology and Neurosurgery and the Montreal Neurological Institute, 1957.
11. Litvak, J., Siderides, L. E., and Vineberg, A. M.: Experimental Production of Coronary Artery Insufficiency and Occlusion, Am. Heart J. **53**: 505-518, 1957.
12. McKeever, D. C.: The Use of Cellophane as an Interposition Membrane in Synovectomy, J. Bone & Joint Surg. **25**: 576-580, 1943.
13. Neumann, C. G., Moran, R. E., von Wedel, J., Lord, J. W., Jr., and Hinton, J. W.: Reduction of Coronary Artery Blood Flow Preparatory to Revascularization of the Heart Via Pedicled Flap of Skin, Plast. & Reconstruct. Surg. **13**: 85-94, 1954.
14. Page, I. H.: Production of Persistent Arterial Hypertension by Cellophane Perinephritis, J. A. M. A. **113**: 2046-2048, 1939.
15. Pearse, H. E.: Experimental Studies on the Gradual Occlusion of Large Arteries, Ann. Surg. **112**: 923-937, 1940.
16. Sutermeister, E., and Browne, F. L.: Casein and Its Industrial Applications, ed. 2, New York, 1939, Reinhold Publishing Corp.
17. Wheeldom, T. F.: Use of Cellophane as Permanent Tendon Sheath, J. Bone & Joint Surg. **21**: 393-396, 1939.
18. Yeager, G. H., and Cowley, R. A.: Studies on the Use of Polythene as a Fibrous Tissue Stimulant, Ann. Surg. **128**: 509-520, 1948.

A DEVICE FOR TIGHTENING LIGATURES

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IN ALL forms of surgery, tying ligatures at great depths has been difficult and at times frustrating. In certain procedures where adequate exposure has been obtained and instrument dissection is possible, there is still inadequate room for accurate hand tying of deep ligatures. To obviate this difficulty, a simple instrument* has been devised (Fig. 1). In various operations it has functioned well, especially in that procedure where exposure is most often difficult—cholecystectomy in the obese patient.

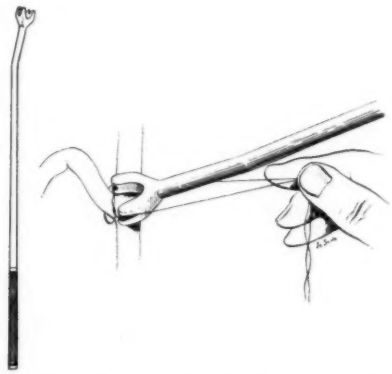

Fig. 1.—Diagram of the instrument and of its use in tying the cystic duct. In its present form the instrument is 12 inches long.

In use, the suture material is passed around the clamp or structure to be tied, by employing a Moynihan or similar forceps. The first knot is tied so that it will lie flat. For right-handed persons, the strings are held in the left hand and the instrument in the right. The instrument pushes the knot down, guiding it to any given place. Then the ligature is tightened. Subsequent knots are fashioned in the same way, tightening each in turn. For the first knot, either a simple or a surgical (double) knot can be used, according to the surgeon's preference. However, the former is simpler and has proved perfectly satisfactory. One theoretical objection to the use of the instrument is that it is impossible to maintain traction on the first knot, while the second one is being tied; however, when tying in deep situations it is rarely if ever possible to maintain tension between knots, and when handling delicate structures it is seldom desirable.

The instrument has been used successfully with all of the common suture materials, but for ease of operation wet chromic catgut was best, silk second,

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*This instrument is available from V. Meuller & Co., Chicago, Ill.

and surgical cotton third. Due to its roughness commercial cotton does not slide easily but it has also been used without complication.

As with any instrument, some practice is needed to acquire skill and confidence in its use. This can easily be obtained by tying knots around a piece of small soft rubber tubing (⅛ or 3/16 inch). This simulates the "give" of tissue, yet its elasticity and hence its tendency to open the knot far exceed that of any human structure.

The advantages of this instrument are most obvious in ligating the cystic duct and artery when performing cholecystectomy. Using the lateral grooves as guides, the knot can be slid up or down the structure until its location is precisely as desired. It can then be tightened under direct vision, assuring one of accurate placement.

SUMMARY

A simple device for tightening ligatures in inaccessible places has been presented and its use illustrated.

ADDENDUM

Since this paper was written, I have found an article by Dr. Henry Byron Larzelere describing a knot tier which embraces some of the principles of the one described herein. The article also summarizes all previous instruments devoted to this purpose. It can be found in SURGERY **27**: 449-456, 1950.

Pediatric Surgery

CONDUCTED BY MARK M. RAVITCH, M.D.

CONGENITAL DIVERTICULUM OF THE ESOPHAGUS

A REPORT OF TWO CASES

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CONGENITAL diverticulum of the esophagus is rare and should not be confused with congenital diverticulum of the posterior hypopharynx which it can simulate both clinically and radiologically. It may occur without other abnormalities or be associated with esophageal stenosis or fistula. When there is an associated stenosis or fistula symptoms occur soon after birth. A diverticulum alone may not be recognized until a complication such as impaction of a foreign body or inflammation occurs. In the Royal Hospital for Sick Children, Glasgow, there have been 2 patients with congenital diverticulum of the esophagus unassociated with other tracheoesophageal abnormalities. One presented when 10 months old although there had been stridor from birth. The other presented at birth. Only two other instances of congenital diverticulum of the esophagus unassociated with other abnormalities have been found in the available literature.

CASE REPORTS

CASE 1.—A. W. M., the third child of healthy parents, was born in February, 1953. The infant had stridor at birth which persisted intermittently thereafter, but he seemed normal in other respects. He did well and gained weight rapidly, but when fed solid food he had difficulty in swallowing and vomiting occurred from time to time from the age of 6 months. During such episodes the stridor became more obvious. When the child was 9 months old, laryngoscopy failed to reveal any abnormality.

On Dec. 7, 1953, at the age of 10 months, he was taken to a pediatric clinic. His weight was 9.1 Kg. In view of the history of stridor from birth and dysphagia when swallowing solid foods, the presence of a vascular ring was suspected and a barium swallow examination was arranged. A straight x-ray of the chest revealed a circular opacity at the level of the second dorsal vertebra which in the lateral view was confirmed as a coin in the upper end of esophagus, although there was no history of one having been ingested. A barium swallow was carried out as planned. This revealed that the coin was lying at the mouth of a pouch leading from the right posterior aspect of the upper third of the esophagus. The esophagus was compressed anteroposteriorly by the pouch, and there was narrowing of the trachea at the level of the coin (Fig. 1).

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A sixpence was removed that evening through an esophagoscope (Dr. M. Joels). Further radiologic investigation of the pouch showed that it possessed a narrow neck which was freely distensible. The mucosal folds of the esophagus continued into the diverticulum which itself showed muscular contraction of its walls, capable of propelling the contained barium into the esophagus (Fig. 2). It was considered that this was an example of a congenital diverticulum of the esophagus which would eventually require surgical removal, but, since the child was thriving well and was causing no undue concern to the parents, operation was delayed.

Fig. 1. Fig. 2.

Fig. 1.—Case 1. Barium swallow showing sixpence at mouth of diverticulum when patient was 10 months old.
Fig. 2.—Case 1. Barium swallow showing diverticulum and compression of esophagus.

The child continued to thrive and remained well until January, 1955, when stridor and dysphagia became marked following the ingestion of carrots. Screening showed that the diverticulum which was distended by nonradiopaque material was compressing the esophagus and trachea. Portions of carrot were removed from the pouch through an esophagoscope. For the next 3 years he continued to thrive and gain weight. He was free from dysphagia except when root vegetables were eaten and stridor seldom occurred. Ingested food passed directly into the esophageal pouch until this was full, and then passed down the esophagus. Peristaltic waves of muscular contraction then emptied the pouch.

Operation (Mr. R. S. Barclay) was performed in June, 1958, since the boy was due to start school that autumn. The pouch was exposed through a left supraclavicular incision. It was firmly adherent to the prevertebral fascia and sharp dissection was necessary to free it. The neck of the pouch was wide and communicated with the esophagus on its posterior aspect 2 cm. from the pharyngoesophageal junction. The pouch was removed and the esophageal wall was repaired with a continuous catgut suture. The wound was closed with drainage and healed rapidly. The boy made an uneventful recovery and

has remained well since with no stridor or regurgitation. A recent barium swallow reveals no obstruction to the flow of esophageal contents and confirms complete removal of the diverticulum (Fig. 3).

The specimen consisted of a diverticulum 2 by 1.5 by 1.5 cm. in size. Microscopically all layers of the esophageal wall were present. The lining was squamous epithelium, and it had circular and longitudinal muscle coats. Lymphoid infiltration in the lamina propia was more marked than usual.

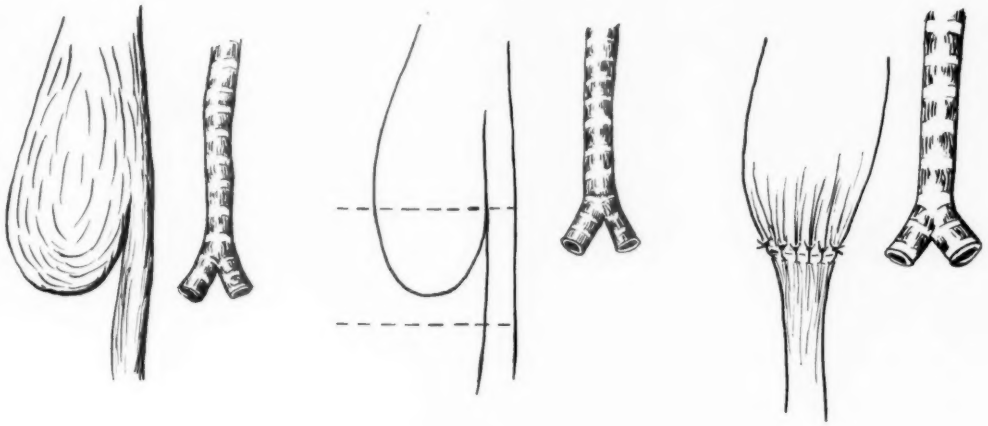
Fig. 3.

Fig. 4.

Fig. 3.—Case 1. Barium swallow following the removal of the diverticulum.
Fig. 4.—Case 2. The diverticulum has been filled with Lipiodol.

Case 2.—J. McL., the second child of healthy parents, was born at Inverness in January, 1959. At birth the infant appeared healthy and weighed 3.1 Kg. Attempts at feeding led to regurgitation and periods of cyanosis. A catheter passed through the mouth was arrested 8 cm. from the gum margin, and following instillation of Lipiodol radiography revealed a large esophageal pouch, the lower border of which was at the level of the sixth dorsal vertebra (Fig. 4). Gas was present in the abdomen. A diagnosis of esophageal atresia with tracheo-esophageal fistula was made and the infant was transferred to the Royal Hospital for Sick Children, Glasgow. The low level of the pouch cast doubt upon the diagnosis, but a repeat x-ray examination confirmed that no Lipiodol passed to the lower esophagus. Operation was performed the same day by one of us (J. C. G.). The right chest was entered through the bed of the resected fourth rib. The mediastinal pleura was incised longitudinally and the azygous vein was divided between ligatures. An esophageal diverticulum was displayed. Its appearance and position was similar to the blind upper pouch of a Vogt[11] Class 3 esophageal atresia, but its fundus was at the level of the carina. There was, however, no interruption in continuity of the esophagus. The esophagus was freed with difficulty from the trachea to which it was intimately adherent, and it was established that no tracheoesophageal fistula existed. Since there was gas in the abdomen, this suggested that the esophagus must be patent, but attempts to lead a catheter through the mouth down the esophagus were unsuccessful. The tip of the catheter invariably lodged in the diverticulum. It was decided that an esophageal stenosis existed and the portion of the esophagus adjacent to the pouch was excised. Through the cut ends of

the esophagus, a catheter could be passed without difficulty upward and downward. There was no stenosis. The dependent part of the pouch was excised. The proximal part of the diverticulum shared a muscle coat with the esophagus and only a mucosal fold which extended upward for about 1 cm. separated the two structures. This mucosal fold was divided longitudinally and the now single-compartment upper esophagus was joined end-to-end to the lower esophagus with a single layer of interrupted silk sutures (Fig. 5, *A*, *B*, and *C*). The mediastinal pleura was closed, a water-seal drain was brought out through an independent incision in the ninth intercostal space, and the chest wound was closed. The child made an uneventful recovery. A barium swallow examination was performed on the twelfth postoperative day (Fig. 6), and apart from slight narrowing at the site of the anastomosis the esophagus appeared functionally and anatomically normal. The fundus of the diverticulum was examined microscopically; the mucosa was squamous epithelium and there were circular and longitudinal layers of muscle. The patient was allowed to go home on the fifteenth postoperative day. Fourteen days later he developed pneumonia and was admitted to Raigmore Hospital, Inverness. He died there on March 17, aged 9 weeks. An autopsy was performed which showed multiple abscesses of the right lung. The suture line of the esophagus had healed and there was no stenosis. There was no fistula between esophagus and trachea. The pancreas was examined microscopically and there was no evidence of fibrocystic disease.



A. *B.* *C.*

Fig. 5.—Case 2. *A*, Appearance of esophagus and diverticulum at operation. *B*, The portion between the dotted lines was excised and the mucosal fold between the esophagus and diverticulum was divided longitudinally. *C*, Appearance at completion of operation.

DISCUSSION

Case 1 closely resembles a case reported by Nelson[7] of a 2-year-old boy who had a history of recurrent upper respiratory infection and progressive dysphagia from 11 months old. On examination he was found to have a penny impacted in an esophageal diverticulum. Partial excision of the diverticulum was performed through a cervical incision. The diverticulum arose from the posterior aspect of the esophagus. Its orifice was nearly 2.5 cm. in longitudinal diameter. Microscopic examination showed that the diverticulum had mucosal, submucosal, and muscle coats.

The other report of this condition is by Jackson and Shallow.[4] Their patient was an 8-year-old boy who presented with a right-sided empyema. He subsequently died and at autopsy was found to have a tubular diverticulum of the esophagus arising from the posterolateral wall 11 cm. from the laryngeal

opening. It was 2.5 cm. long, 4 cm. in diameter, and the same caliber throughout its length. Microscopic examination of the wall showed that it contained mucosal, submucosal, and muscular layers corresponding with those of the esophagus.

Knox[6] and Robb[9] have each reported one case in which there was an esophageal diverticulum and an associated tracheoesophageal fistula and both O'Bannon[8] and ten Kate[5] reported one case of esophageal diverticulum with an associated esophageal stenosis. Gross[3] describes a patient with an esophageal stenosis in whom the stenotic area arose from the side of the dilated upper esophagus. The portion of dilated upper esophagus distal to this side opening could be called a diverticulum.

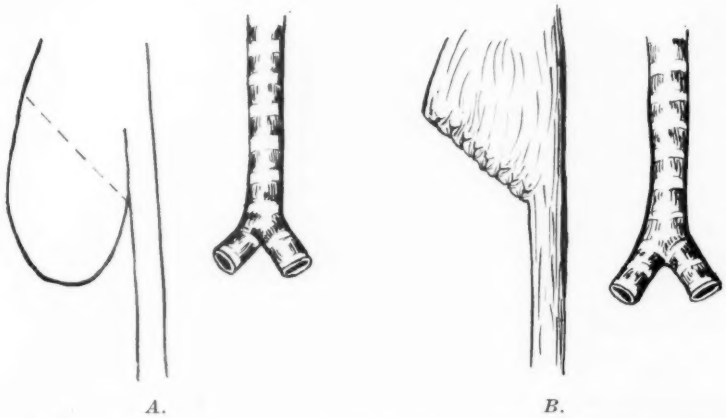
Fig. 6.—Case 2. Barium swallow on the twelveth postoperative day showing satisfactory anastomosis.

Case 2 is similar to these cases, but there was neither stenosis nor tracheoesophageal fistula. The similarity, however, has led us to believe that congenital diverticulum of the esophagus is yet another variation of the tracheoesophageal anomalies, the commonest of which (Class 3 in Vogt's classification[11]) has a blind upper esophagus and the lower esophagus communicates with the trachea near the carina.

In the more common condition of congenital diverticulum of the posterior hypopharynx, the diverticulum arises from the midline posteriorly just above the cricopharyngeal junction and passes into the thorax behind the esophagus. Its wall contains a muscle coat. Such cases have been reported by Brintnall and Kridelbough,[1] Duhamel,[2] and Rouchy[10] where the patients presented as

neonatal emergencies with a history of regurgitation of feedings and were mistakenly diagnosed as cases of esophageal atresia. If a catheter is passed through the mouth and enters the diverticulum, it is arrested, and, should a radiograph be taken after instillation of Lipiodol, a pouch will be demonstrated which is indistinguishable from the blind upper esophagus in a case of esophageal atresia.

In Case 1 there was a history of stridor from birth and dysphagia from the time the patient was given solid food. The sixpence, impacted at the mouth of the diverticulum, may have aggravated the symptoms but they were caused mainly by the pressure of the diverticulum, when full of food, on the esophagus and trachea. When the patient was given a diet free of solid material, he remained symptom free. The advantages of delaying operation until the child was older are not great. If operation had been performed once the necessity for operation was recognized, the child and his parents would have been spared the long period of special feeding, and the dangers of regurgitation and aspiration during this period would have been eliminated.



A. *B.*

Fig. 7.—*A* and *B*, Drawings to illustrate an alternative method of dealing with Case 2 which would have preserved the continuity of the esophagus.

In Case 2 the mucosal flap which separated the proximal part of the diverticulum from the esophagus acted as a valve and, when the diverticulum filled, the esophagus was obstructed. The lesion might have been demonstrated preoperatively if screening had been done with the child in different positions. The operative procedure which was adopted was satisfactory, although in fact it was unnecessary to cut across the esophagus (this was done because stenosis was thought to be present). It would have been possible to excise the lateral and lower portions of the diverticulum and thus preserve the continuity of the esophageal wall. The displayed mucosal flap could be excised then and the esophageal wall repaired by a row of longitudinal sutures (Fig. 7, *A* and *B*).

When operation for this condition is undertaken, the choice of a thoracic or a cervical approach must depend upon the level of the pouch, but it should be borne in mind that only a partial excision of the diverticulum was possible through a cervical incision in Nelson's patient.[7] Moreover, these lesions may be associated with tracheoesophageal fistulas which would be difficult to demonstrate and deal with through a cervical incision.

SUMMARY

Congenital esophageal diverticulum, unassociated with other esophageal abnormalities, has been reported twice before. Two additional cases are presented. In one at the age of 5 years, through a cervical approach, an esophageal diverticulum was completely excised in a child who had had a lifelong history of stridor and dysphagia. The second was a newborn infant whose filled diverticulum obstructed the esophagus and created the illusion of esophageal atresia. The esophagus was transected, the septum between diverticulum and esophagus was divided, and the esophagus was reanastomosed. A primary stricture-free union resulted. The child died at the age of 9 weeks, at another hospital, of multiple pulmonary abscesses, although autopsy showed no stricture or fistula.

Although the particular operation chosen in Case 2 seems not to have been involved in his ultimate death, a simpler operation would have been feasible and is described.

It is suggested that in spite of the absence of any other esophageal abnormalities these patients may represent yet another variation of the tracheoesophageal anomalies, the commonest of which is esophageal atresia with tracheoesophageal fistula.

Case 1 was a patient in Professor Stanley Graham's wards and Case 2 in Mr. Wallace Dennison's wards. We wish to acknowledge our appreciation to our colleagues on the Staff of the Royal Hospital for Sick Children, Glasgow, and elsewhere for their cooperation in the investigation and treatment of these patients.

The drawings were done by Mrs. J. C. Wood.

REFERENCES

1. Brintnall, E. S., and Kridelbough, W. W.: Congenital Diverticulum of the Posterior Hypopharynx Simulating Atresia of the Esophagus, Ann. Surg. **131:** 564, 1950.
2. Duhamel, B.: Deux cas de diverticules congenitaux de l'oesophage cervical. Considerations sur le diagnostic des malformations congenitales de l'oesophage, Arch. franç. pédiat. **6:** 499, 1949.
3. Gross, R. E.: The Surgery of Infancy and Childhood, Philadelphia, 1953, W. B. Saunders Company.
4. Jackson, C., and Shallow, T. A.: Diverticula of the Esophagus, Pulsion Traction, Malignant and Congenital, Ann. Surg. **83:** 1, 1926.
5. ten Kate, J.: Congenital Diverticulum of Oesophagus, Arch. chir. neerl. **4:** 277, 1952.
6. Knox, G.: Congenital Tracheoesophageal Fistula Without Esophageal Atresia, SURGERY **30:** 1016, 1951.
7. Nelson, A. R.: Congenital True Esophageal Diverticulum: Report of a Case Unassociated With Other Esophago-tracheal Abnormality, Ann. Surg. **145:** 258, 1957.
8. O'Bannon, R. P.: Congenital Partial Atresia of Esophagus Associated With Congenital Diverticulum of Esophagus; Report of a Case, Radiology **47:** 471, 1946.
9. Robb, D.: Congenital Tracheoesophageal Fistula Without Atresia but With Esophageal Diverticulum, Australia & New Zealand J. Surg. **22:** 120, 1952.
10. Rouchy, R., Creze, J., and Courtillie, P.: Diverticule congenital de l'oesophage chez un nouveau-ne, Bull. Féd. soc. gynéc. et obst. **6:** 103, 1954.
11. Vogt, E.: Congenital Esophageal Atresia, Am. J. Roentgenol. **22:** 463, 1929.

CONGENITAL SMALL INTESTINAL STENOSIS AND ATRESIA

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EXPERIENCES with the operative treatment of congenital small intestinal stenosis and atresia in this institution were reviewed some years ago by Moore and Stokes[4] and by Moore.[3] The operative mortality was encouragingly low in cases of duodenal obstruction but disappointingly high in cases of jejunal and ileal atresia. In the past few years advances in the surgical management of jejunal and ileal atresia have been reported by Gross[2] and Gerrish.[1] We have been prompted to bring our experiences up to date in order to learn whether the earlier good results with duodenal obstruction have been maintained and whether improvement has been achieved with the more distal obstructions. Only cases treated from 1942 through 1958 are considered.

DUODENAL STENOSIS AND ATRESIA

Twenty-five cases of duodenal stenosis and atresia have been treated (Table I). There were 16 cases of atresia and 9 of stenosis. Fourteen were in females and 11 in males. The average age of those with atresia was a little over 5 days at the time of operation. Four of those with stenosis were less than a week old; the other 5 ranged in age from 16 days to 7 months. There were associated anomalies in 4 patients with duodenal stenosis—cleft palate, umbilical hernia, Mongolism, and a peritoneal band. Five of the 16 with duodenal atresia were born prematurely; two of these had other anomalies, one, an imperforate anus and the other, an esophageal atresia with tracheoesophageal fistula. Five additional patients had associated anomalies—two, malrotation; one, malrotation and Mongolism; one, the inspissated bile syndrome; and one, esophageal atresia with tracheoesophageal fistula. Thus of the total 25 cases, 14 (56 per cent) were born prematurely or had some associated congenital anomaly.

Six of them required operation for the associated anomaly. All except one recovered uneventfully, though one died at 6 months of age of pneumonia and resultant multiple lung abscesses. The exceptional case was that of a premature infant who withstood division and ligation of a tracheoesophageal fistula and esophageal anastomosis for atresia only to expire shortly after duodenojejunostomy and gastrotomy were carried out on the day following the first procedure. Two patients had undergone operation prior to admission. In one, a gastroileostomy had been performed through error. He did well after the

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TABLE I. RESULTS OF TREATMENT OF DUODENAL STENOSIS AND ATRESIA

CASE NUMBER	YEAR	SEX AND AGE AT SURGERY	SITE AND CHARACTER OF OBSTRUCTION	ASSOCIATED ANOMALY	OPERATION	RESULT	REMARKS
Cases which required no other operation and had received no operative treatment prior to admission							
1	1942	Female 3 days	Stenosis distal duodenum	Cleft palate	Gastrojejunostomy	Recovered	Living and well, cleft palate repaired later
2	1946	Male 5 weeks	Stenosis distal duodenum	Umbilical hernia	Gastrojejunostomy	Recovered	Living and well
3	1949	Female 4 days	Atresia distal duodenum		Duodenojejunostomy	Recovered	Living and well
4	1951	Male 3 weeks	Stenosis distal duodenum		Duodenojejunostomy	Recovered	Living and well
5	1951	Male 7 months	Stenosis distal duodenum		Duodenojejunostomy	Recovered	Living and well
6	1952	Male 3 days	Atresia distal duodenum		Duodenojejunostomy	Died	Died 1 day postoperatively, hyperpyrexia; subarachnoid hemorrhage at autopsy, anastomosis intact
7	1952	Male 2 days	Atresia distal duodenum		Duodenojejunostomy	Recovered	Living and well
8	1953	Female 5 days	Atresia distal duodenum		Duodenojejunostomy	Recovered	Living and well
9	1953	Female 5 days	Atresia proximal duodenum		Duodenojejunostomy	Recovered	Living and well
10	1953	Female 16 days	Stenosis distal duodenum		Duodenojejunostomy	Recovered	Living and well
11	1953	Male 5½ months	Stenosis distal duodenum	Mongolism	Duodenojejunostomy	Recovered	Admitted with sudden hematemesis; no cause found; uneventful postoperative course, now lost to follow-up
12	1954	Female 3 days	Stenosis distal duodenum		Duodenojejunostomy	Recovered	Living and well

13	1955	Female 11 days	Atresia middle duodenum	Premature	Duodenojejunostomy	Recovered	Living and well
14	1955	Female 6 days	Atresia proximal duodenum	Premature	Gastrojejunostomy	Recovered	Living and well
15	1955	Female 6 days	Stenosis middle duodenum		Duodenojejunostomy	Recovered	Normal postoperative course, now lost to follow-up
16	1955	Male 6 days	Atresia middle duodenum	Premature	Duodenojejunostomy	Died	Jaundice following surgery; died on ninth postoperative day with massive gastrointestinal bleeding; ? hypoprothrombinemia; autopsy disclosed common duct stenosis at ampulla of Vater; no focal bleeding points
17	1955	Female 6 days	Atresia proximal duodenum		Duodenojejunostomy	Recovered	Living and well
			Cases treated by operation prior to admission and requiring reoperation				
1	1952	Male 12 days	Atresia middle duodenum	Malrotation of intestine	Duodenoduodenostomy	Recovered	Severe malnutrition on admission; gastroileostomy had been carried out elsewhere at age 4 days; gastroileostomy taken down at time of duodenoduodenostomy; living and well
2	1958	Male 7 days	Stenosis distal duodenum	Peritoneal band	Duodenojejunostomy	Recovered	Lysis of adhesive bands at age 3 days elsewhere; re-explored here age 7 days; gastrostomy performed because of suspected meconium ileus; operation 6 days later; generalized peritonitis subsequent to leak around gastrostomy tube; living and asymptomatic
			Cases requiring operative treatment for associated anomalies				
1	1946	Female 6 days	Atresia proximal duodenum	Imperforate anus; premature	Gastrojejunostomy	Recovered	Duodenal and anorectal obstruction repaired successfully; did well until age 6 months, at which time she contracted pneumonia, multiple lung abscesses, and expired

TABLE I. (CONT'D)

CASE NUMBER	YEAR	SEX AND AGE AT SURGERY	SITE AND CHARACTER OF OBSTRUCTION	ASSOCIATED ANOMALY	OPERATION	RESULT	REMARKS
2	1950	Female 4 days	Atresia proximal duodenum	Esophageal atresia with tracheoesophageal fistula; premature	Duodenojejunostomy	Died	Gastrostomy and duodenojejunostomy carried out 24 hours after extrapleural ligation of tracheoesophageal fistula and end-to-end esophageal anastomosis; died shortly after second operation; anastomosis intact
3	1951	Male 5 days	Atresia proximal duodenum	Malrotation of intestines; Mongolism	Gastrojejunostomy	Recovered	Good postoperative course; now lost to follow-up
4	1955	Male 6 days	Atresia proximal duodenum	Inspissated bile syndrome	Duodenojejunostomy	Recovered	Common duct exploration revealed inspissated bile syndrome; relieved of jaundice
5	1956	Female 10 days	Atresia distal duodenum	Malrotation of intestines	Duodenojejunostomy	Recovered	Living and well
6	1957	Female 3 days	Atresia distal duodenum	Esophageal atresia with tracheoesophageal fistula; premature	Duodenojejunostomy	Recovered	Ligation of tracheoesophageal fistula and primary esophageal anastomosis at age 3 days; the following day, gastrostomy and duodenojejunostomy; six days later repair of partial disruption of abdominal wound; remainder of postoperative course essentially uneventful; now undergoing periodic esophageal dilatations; doing well

gastroileal anastomosis was taken down and a duodenojejunostomy was performed. The other had been explored and subjected to lysis of congenital intraperitoneal bands at the age of 3 days. On exploration here he was thought to have meconium ileus and a gastrostomy was carried out. The correct diagnosis was established shortly afterward and a duodenojejunostomy performed uneventfully. The remaining 17 cases had their initial operation here. In the two earliest cases gastrojejunostomy was performed and one later patient was treated in the same fashion by a member of our visiting staff. In all the others, duodenojejunostomy was carried out. There were two fatalities. One premature male infant developed jaundice postoperatively and expired on the ninth day from massive gastrointestinal bleeding. Autopsy disclosed stenosis of the common duct at the ampulla of Vater. No bleeding point could be identified. The other died of subarachnoid hemorrhage on the day following operation. Thus, of the entire group of 25, there were 3 deaths, a mortality of 12 per cent.

JEJUNAL AND ILEAL ATRESIA

During the years covered by this study, 16 patients were treated for jejunal or ileal atresia. There were no cases of stenosis of the jejunum or ileum. The atresia involved the ileum alone in 5 cases, the jejunum alone in 6. One had atresia of the proximal and stenosis of the distal jejunum. In one patient there were atretic areas in both jejunum and ileum and in another the entire jejunum and all but one inch of the ileum were involved in this process. Two had atresia of the ascending colon; the other atretic segment was jejunal in one, ileal in the other. Eight patients were males and 8 were females. Sixteen were 7 days of age or less (average 3.5), while one was 20 and another 30 days old at the time of treatment. Six were born prematurely; three of them had additional anomalies—malrotation, malrotation and midgut volvulus, and malrotation and gastroschisis. Four other infants had other anomalies. One had a club foot; another, congenital evisceration of unknown cause; and another, malrotation of the colon. The fourth had meconium ileus, cystic fibrosis of pancreas, and extrahepatic biliary atresia. Thus, prematurity or other obvious anomaly was present in 10 of the 16 (62.5 per cent).

In the first 11 cases resection or a bypassing anastomosis was carried out without a proximal decompressive enterostomy. In two, a breakdown of the anastomosis occurred with fatal peritonitis (Cases 2 and 8). Two patients developed early stenosis of the anastomotic site and required reoperation. One expired a month afterward, the other at the age of 2½ months (Cases 7 and 9). A third had to be operated upon 3 years later because of an anastomotic stricture. She has done well. In the remainder the anastomosis was satisfactory. Of the entire group of 11, however, only 2 survived (Cases 5 and 10). A colonic atresia was not recognized at the first operation in one case. This child died 2 days after this additional anomaly was recognized and treated on the sixth day following the original surgical procedure (Case 6). One very ill, premature infant with multiple atresias, gastroschisis, and malrotation survived only 3 days. In another case, evidence of intestinal obstruction developed 2 weeks after the initial procedure and death occurred 2 days after exploration

TABLE II. RESULTS OF TREATMENT FOR JEJUNAL AND ILEAL ATRESIA

CASE NUMBER	YEAR	SEX AND AGE AT SURGERY	SITE OF ATRESIA	ASSOCIATED ANOMALY	OPERATION	RESULT	REMARKS
				No proximal decompressive enterostomy			
1	1948	Female 6 days	Jejunum	Premature; malrotation and midgut volvulus	Resection atretic segments; duodenojejunostomy	Died	Developed obstruction from adhesions 14 days postoperatively, died 2 days after second operation; anastomosis intact
2	1948	Female 3 days	Jejunum	Club foot	Resection atretic segment; jejunojejunostomy	Died	Died 3 days postoperatively; breakdown anastomosis; perforation of distal jejunum; peritonitis
3	1949	Female 5 days	Jejunum	Meconium ileus; cystic fibrosis of pancreas; extrahepatic biliary atresia	Jejunojejunostomy	Died	Re-exploration 10 days postoperatively; obstruction due to meconium ileus; ileocolostomy; died; perforation of ileum
4	1951	Female 20 days	Ileum and ascending colon	Gastroschisis; malrotation; premature	Ileotransverse colostomy	Died	Died 3 days postoperatively; anastomosis intact
5	1951	Female 1 month	Ileum	Congenital evisceration	Resection and ileoascending colostomy	Recovered	Congenital evisceration of unknown cause repaired and ileostomy performed elsewhere; progressive inanition up to time of admission; well
6	1952	Male 2 days	Jejunum, ascending colon	Premature	1. Jejunojejunostomy 2. Resection and ileotransverse colostomy	Died	Colonic atresia not recognized at initial operation; reoperation 6 days later, expired in 2 days; both anastomoses intact
7	1952	Female 4 days	Jejunum ileum	Malrotation; premature	Resection atretic segments; jejunoileostomy	Died	Anastomosis stenotic; reoperation 6 days later; did well; gained weight; sudden unexplained death 1 month later; anastomosis intact
8	1953	Male 2 days	Jejunum		Resection atretic areas; jejunoileostomy	Died	Evisceration and breakdown of anastomosis 4 days postoperatively; died 1 day later

9	1954	Male 3 days	Distal ileum		Resection and ileocolostomy	Died	Developed obstruction at anastomotic site and reoperated upon 13 days postoperatively; exteriorization procedure; revision 12 days later; ileocolostomy 18 days later; downhill course; died at age of 2½ months
10	1954	Female 6 days	Jejunum	Malrotation	Resection; jejunojejunostomy	Lived	Good initial result; reoperation 3 years later for anastomotic stricture; living and well
11	1956	Male 3 days	Almost all jejunum and ileum		Duodenoileostomy	Died	Less than one inch small intestine below ligament of Treitz; transit time mouth to anus 2½ minutes; progressive malnutrition; died at 3 weeks of age
				Proximal decompressive enterostomy			
1	1956	Male 2 days	Ileum	Partial midgut volvulus	Resection, ileoileostomy, proximal ileostomy	Recovered	Recovery; well
2	1956	Male 3 days	Ileum		Ileoileostomy; proximal ileostomy	Recovered	Ileostomy tube left in 2½ months; surgical closure ileostomy; well
3	1957	Female 7 days	Jejunum	Premature, 3 lb., 6 oz.	Resection, jejunojejunostomy; proximal jejunostomy, gastrostomy	Recovered	Recovery; well
4	1958	Male 2 days	Jejunum		Resection, jejunojejunostomy; proximal jejunostomy	Recovered	Recovery; well
5	1958	Male 1½ days	Ileum	Premature, 3 lb., 2½ oz.	Resection, ileoileostomy, proximal ileostomy	Died	Did well until anastomotic stenosis developed 6 weeks postoperatively; severe dehydration and electrolyte imbalance before corrective therapy was instituted; reoperation; resection, anastomosis, proximal ileostomy; expired 24 hours later

and lysis of adhesions (Case 1). The remaining patient had a hopeless situation, only one inch of small intestine beyond the ligament of Treitz. After duodenal-ileal anastomosis the transit time from mouth to anus was only 2½ minutes. This infant exhibited progressive malnutrition and expired when 3 weeks old.

In the last 5 cases a proximal decompressive enterostomy was utilized. The results were much better. Four recovered and the fifth, a premature infant weighing only 3 pounds, 2½ ounces, did well for 6 weeks after operation. Evidence of anastomotic stenosis then developed and death occurred after the second operative procedure.

DISCUSSION

In our hands the management of duodenal stenosis and atresia has continued to be satisfactory. Only 3 of the 25 treated patients died, a mortality of 12 per cent. One had undergone a repair of a tracheoesophageal fistula and esophageal atresia. Another died of a subarachnoid hemorrhage and the third of massive gastrointestinal bleeding associated with jaundice, possibly resulting from stenosis of the ampulla of Vater. Although an occasional infant does well with gastrojejunostomy, duodenojejunostomy is certainly the operation of choice.

During the latter part of the period covered by this survey encouraging contributions have been reported by Gross[2] and by Gerrish[1] in the treatment of jejunal and ileal atresia. The former was able to treat 6 of 7 patients successfully by performing an exteriorization procedure first and carrying out an intestinal anastomosis 2 weeks later. The latter managed with success 7 of 10 cases by primary anastomosis and proximal decompressive tube enterostomy. When this principle was applied we noted a dramatic change in survival rate. Four of 5 patients left the hospital in good condition and the fifth did well for 6 weeks, only to succumb to a second operation necessitated by the development of an anastomotic stenosis. In contrast, there were only 2 long-term survivors of the 11 previously treated by resection or bypass without decompressive enterostomy.

An analysis of these 11 earlier experiences tends to confirm the importance of adequate proximal decompression since two of these infants died as the result of anastomotic breakdown. That failure to provide proximal decompression was not responsible for the other deaths is evident. Two died a month and 2 months, respectively, after the original procedure following reoperation for stenosis at the site of anastomosis. Five died with satisfactory anastomoses —one after a second operation for an initially unrecognized colonic atresia, one because there was insufficient small intestine for adequate nutrition, one following a secondary operation for intestinal obstruction due to adhesions, one a few days after correction of multiple atresias, malrotation, and gastroschisis, and one died with biliary atresia and a perforated ileum due to meconium ileus.

Our experience emphasizes the importance of a carefully performed anastomosis between the dilated proximal and the diminutive distal segment since two of the deaths in the first group and the only death in the latter were

the direct consequence of anastomotic stenosis and its necessary operative correction. There is no sure solution to this problem. At present we feel that factors of apparent primary importance include an anastomosis of maximal size and a carefully performed one-layer anastomosis using interrupted fine nonabsorbable arterial sutures. Our experiences also point out the importance of careful exploration at the initial operation with correction of all existing anomalies. They demonstrate further that failure will necessarily occur occasionally because of inadequate length of functioning intestine and will very likely occur from time to time because of the multiplicity of defects requiring surgical correction. We are convinced, as are Gross and Gerrish, that adequate decompression of the proximal dilated intestine is a really important safeguard. Only further experience will tell whether an initial exteriorization procedure or a primary anastomosis with tube enterostomy yields better results. For the present we are inclined to continue utilizing the latter method.

SUMMARY

1. Twenty-five cases of duodenal atresia treated between 1942 and 1959 had an over-all survival rate of 88 per cent. Duodenojejunostomy is the procedure of choice.

2. The long-term survival rate was poor (18 per cent) in the first 11 cases of jejunal or ileal atresia treated during this period. It was much better (80 per cent) in the last 5 cases in which a proximal tube decompressive enterostomy was employed as an adjuvant to resection or bypass. Proximal decompression is obviously important since nearly one-fourth of the earlier deaths resulted from anastomotic breakdown. Factors other than failure to provide adequate decompression, however, were responsible for the majority of these earlier fatalities. A matter of obvious importance is the construction of an anastomosis which is likely to maintain adequate patency.

REFERENCES

1. Gerrish, E. W.: Operative Management of Congenital Intestinal Atresia, Ann. Surg. **142**: 469, 1955.
2. Gross, R. E.: Surgery of Infancy and Childhood, Chapter 11, Philadelphia, 1955, W. B. Saunders Company.
3. Moore, T. C.: Congenital Intrinsic Duodenal Obstruction, Ann. Surg. **142**: 159, 1956.
4. Moore, T. C., and Stokes, G. E.: Congenital Stenosis and Atresia of the Small Intestine, Surg. Gynec. & Obst. **97**: 719, 1953.

Recent Advances in Surgery

CONDUCTED BY ALFRED BLALOCK, M.D.

EXPERIENCES WITH MINIMAL WOUND DRESSINGS FOLLOWING HEAD AND NECK SURGERY

CONSTANT SUCTION USED IN LIEU OF BULKY WOUND DRESSINGS

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SURGEONS are constantly searching for more effective methods of dressing wounds. It has long been the custom following extensive surgery about the head and neck to apply large bulky compressive dressings which are usually extremely uncomfortable for the patient and quite often interfere with wound healing. Some surgeons feel it is mandatory to routinely apply pressure dressings in head and neck surgery following any extensive operation on the neck such as a neck dissection or a neck dissection combined with the removal of a tumor within the mouth or larynx. It was thought that these bulky dressings should be used to give an even elastic pressure over the skin flaps. Some surgeons even advocated that the rubber bag from the cuff of the blood pressure machine should be incorporated with the dressing and inflated to about 30 mm. Hg to provide a more adequate elastic pressure. These pressure dressings were thought to diminish the accumulation of blood and serum in the wound spaces and to absorb the often copious wound discharges. It has been stated that loosely applied dressings over the wounds in neck dissection would almost invariably result in complications beginning with the accumulation of blood clots and serum in the loose space beneath the mobilized flaps with edema from passive congestion in the flaps themselves. Oftentimes the very complications the pressure dressings are supposed to prevent were increased in severity by the dressings. Maceration of the underlying skin will frequently occur because of the constant saturation of the dressings with wound secretions. Adequate pressure applied to bulky dressings in the region of the neck is usually quite uncomfortable to the patient and often increases the tendency toward edema.

Following extensive surgery about the neck and head, particularly when the mouth must be entered in continuity, a tracheostomy is necessary in the immediate postoperative period. The management of this tracheostomy is made doubly difficult during this postoperative period when large bulky

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dressings are applied. Frequent changes of dressings increase the patient's discomfort and can easily interfere with adequate immobilization of areas recently grafted with skin.

Approximately 10 years ago, the late Dr. Grant E. Ward and I first became interested in the possible use of constant suction applied beneath the skin flaps in place of compression dressings. Following the use of this method in the first case, which was a bilateral neck dissection with in-continuity laryngectomy, we were immediately impressed with its advantages. It has been used on all feasible subsequent cases in surgery about the head and neck.

PROCEDURE

The subjects of this report were for the most part the ones who underwent some form of "composite" or "commando" type operation. Some were subjected to a radical neck dissection alone. The remaining patients are listed in the thyroidectomy group. No attempt was made to select patients other than to use suction in the cases listed above. Two suction catheters were used in all cases except in those patients that had undergone a parotidectomy. In this instance only one suction tube was inserted beneath the cheek flap (Fig. 1).

Following the completion of the neck dissection or neck part of a composite operation, two multiple perforated No. 16 or No. 18 French rubber catheters of appropriate length were inserted through separate stab wounds and tunneled beneath the skin in the infraclavicular area. The stab wounds were usually placed one on each side of the vertical incision. The tip of one catheter was directed upward to rest in the region of the mastoid; the other assumed a more medial course to rest in either the submental area or the opposite mastoid region. The catheters were sutured in place loosely with a very fine catgut suture (Fig. 2).

In the case of parotid dissections one catheter is tunneled beneath the skin from a separate stab wound inferior to the medial tip of the incision and made to lie in front of the ear throughout the length of the incision. The catheters are anchored to the skin at the stab wound with black silk sutures. It was thought important immediately to attach the catheters to constant suction at 30 mm. Hg as soon as they had been placed in order to prevent the clotting of stagnant blood within the lumen of the catheters, which would negate the expected use of the catheters. Where two catheters were used, they were connected to a single suction unit with a sterile "Y" glass connecting tip. When suction had been established the skin flaps were closed in the routine manner, and, if a composite operation were being done, the oral part of the procedure was carried out. Just before the completion of the operation and removal of the drapes the suction was discontinued and the suction tubes were gently flushed with warm saline solution to rinse out any blood clots. When the skin flaps had been closed the skin edges were washed with ether, collodion, or some of the new plastic sprays, such as Aeroplast, applied to the skin edges. One thin film of narrow-mesh gauze

was then placed immediately over the skin incisions and collodion or plastic again applied. If the collodion or plastic showed signs of rubbing off a new coating was immediately applied (Fig. 3).

As soon as suction is applied to an airtight incision, one is immediately impressed by how the skin flap closely adheres by suction to the underlying denuded surfaces (Fig. 4). Suction is maintained on the average from 36 to 72 hours. At the end of 36 hours, the suction tubes are clamped and suction is discontinued for a period of 6 hours, at which time suction is again established and the accumulation of material in the suction receptacle is carefully measured. If this is no more than a few cubic centimeters, the suction tubes are removed and the stab wounds are covered with small Band-Aids. If the accumulation of serum is more than a few cubic centimeters, suction is re-established for another 36 hours.

If skin grafting is done, definitive pressure is obtained immediately over the graft with a classical stint dressing tied over the graft with the long ends of the black silk sutures used to suture the skin graft in place. We have preferred to use cotton soaked with aqueous Zephiran to form a molded stint. Occasionally, however, a Barton "head-dressing" has been applied over a mandibular defect for immobilization when a hemimandibulectomy has been done as part of the procedure. This is used to prevent immediate displacement of the remaining mandibular fragment and is usually discontinued at the same time that the suction tubes are removed.

The suction method of dressing has been used in 418 cases. No systemic reactions were noted. Five cases were judged as failures. Two of these were due to the loss of suction due to the lack of an airtight closure of the skin flaps. In the "composite" operation group there were 3 instances of severe infection—one a hemolytic staphylococcus infection, the others *Pyocyaneus aerogenes* infections. It is difficult to attribute the infections to the suction principle alone. The types of wounds treated are summarized in Table I.

TABLE I

TYPE OF OPERATION	NUMBER OF CASES	COMPLICATIONS
Parotidectomy	100	0
Radical neck dissection	75	2
Bilateral neck dissection	12	0
Composite operation (intraoral primary)	150	3
Composite operation (larynx primary)	46	4
Radical neck with thyroidectomy	35	0

The 2 cases listed as complications following the use of suction after the simple radical neck dissection represented a reaccumulation of serum beneath the skin flaps. There were 7 instances of fistulas when suction was used after composite operations; all but one of these closed spontaneously.

Postoperative wound suction has also been used with excellent results in numerous cases in other than the head and neck region, e.g., in radical mastectomy, hemipelvectomy, shoulder girdle amputations, and femoroinguinal iliac node dissection.

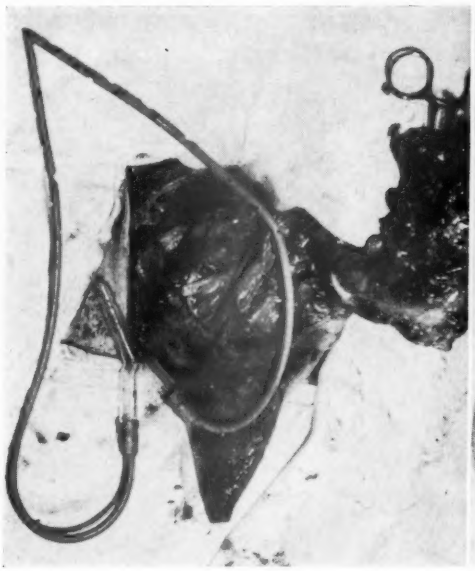

Fig. 1.

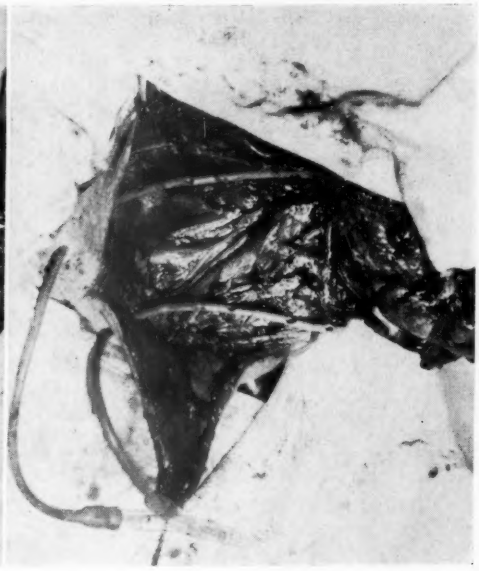

Fig. 2.

Fig. 1.—Neck dissection completed. Specimen still attached to primary cancer of tongue.
Fig. 2.—Suction tubes in place.

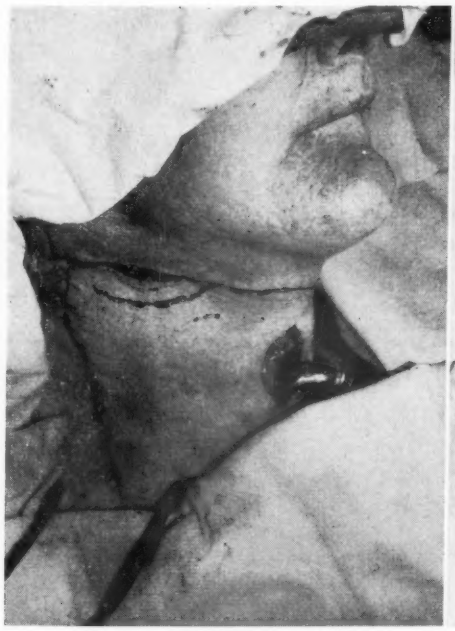

Fig. 3.

Fig. 4.

Fig. 3.—Skin flaps closed. Neck tissues (right radical neck and left supraomohyoid) have been removed along with the right tongue and floor of mouth structures.
Fig. 4.—Suction has been started. Note the complete collapse of the skin flap with obliteration of all dead space.

For the most part the immediate adherence of the skin flap is maintained adequately once suction had been applied. However, in some of the patients, that is, those who had an extensive amount of adipose tissue or in whom the wound showed evidence of poor hemostasis, adequate suction was not maintained and the skin flaps tended to elevate. Fifteen of the composite operations required supplementary localized gauze pressure and flushing of the catheters. The response to these measures was usually satisfactory.

A satisfactory result is defined as a wound which required no particular care to the suction; showed no evidence of erythema, infection, or necrosis; and healed rapidly with the skin flaps adhering to underlying tissue constantly so that the skin sutures could be removed on the fifth or sixth day. Eighty-six per cent were satisfactory; 1 per cent required supplementary gauze compression, 5 per cent exhibited some complications.

DISCUSSION

The objections to the classical method of dressing wounds about the head and neck are legion and need not be repeated. Both surgeons and patients would welcome a dressing easily applied which subjects the patient to no discomfort in its application, maintenance, or removal and which permits complete mobilization of the head and neck, and constant observation of the wound from day to day without removal of the dressing, yet, at the same time provides mechanical adherence of large skin flaps to underlying surfaces and offers adequate bacteriologic protection. The experience with the use of suction beneath skin flaps and plastic applied to skin edges indicates that this method is satisfactory in all these respects. The instance of complications is no greater than with older tried and true multigauze dressings and cannot be attributed to the suction itself.

CONCLUSION

Postoperative wound suction seems to hasten the recovery period in any instance when large masses of tissue have been removed. This form of minimal wound dressing is much more comfortable for the patient and allows the maximum of motion and mobilization without significant effects.

REFERENCES

1. Brown, J. B., and McDowell, F.: Neck Dissection, Springfield, Ill., 1954, Charles C Thomas, Publisher.
2. Davis, J. S.: Plastic Surgery, Philadelphia, 1919, P. Blakiston's Son & Co.
3. Martin, H.: Surgery of Head and Neck Tumors, New York, 1957, Paul B. Hoeber, Inc.
4. Ward, G. E., and Hendrick, J. W.: Tumors of the Head and Neck, Baltimore, 1951, The Williams & Wilkins Company.
5. Wise, R. A., and Baker, H. W.: Surgery of the Head and Neck, Chicago, 1958, Year Book Publishers, Inc.

INTRACARDIAC SURGERY EMPLOYING HYPOTHERMIA AND CORONARY PERFUSION PERFORMED ON 100 PATIENTS

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CIRCULATORY stasis under hypothermia and the use of a cardiopulmonary bypass are the two methods currently used for open cardiac surgery. Hypothermia has several advantages for the repair of some defects, but its use is limited by the short tolerable period of circulatory stasis if body temperature is only slightly lowered or by the increasing incidence of spontaneous serious arrhythmia with more vigorous cooling. In early clinical experiences body temperature was often lowered to 25° C. but more recently 28° C. has become a popular lower limit, above which serious spontaneous arrhythmia is rare. At 29° to 31° C. the heart will tolerate 6 to 8 minutes of circulatory stasis, but because of myocardial ischemia longer periods are associated with a high incidence of ventricular fibrillation. The safe period of myocardial ischemia can be prolonged by reducing the myocardial oxygen requirement with induced cardiac arrest.[2] On the other hand, the myocardium can be easily perfused selectively while the rest of the circulation is stopped. With either of these methods the limiting factor becomes the tolerance of the brain, rather than the heart, for ischemia; although exact data are not available, cerebral circulation probably can be interrupted safely in the human for 12 to 14 minutes at 28° C. Studies by Brockman and Fonkalsrud[3] with cardiac arrest showed no gross neurologic injury in dogs unless occlusion periods were greater than 20 minutes at 28° C.

Coronary perfusion has a distinct advantage over induced cardiac arrest in that the cardiac action is maintained during venous occlusion. Accordingly, when the venae cavae are released, the heart is immediately able to pump the sudden influx of blood. A systolic femoral arterial pressure of 120 to 150 mm. Hg is often obtained within a few seconds after release of the caval occlusion. This is in contrast to a period of hypotension which may follow resumption of circulation after circulatory stasis without coronary perfusion.

Our initial experiences with circulatory arrest and coronary perfusion were reported in 1957.[8] This report describes results obtained with 100 patients operated upon for atrial septal defect or pulmonic stenosis and is presented to support our present belief that hypothermia is a simple and safe means of allowing repair under direct vision of simple atrial defects or valvular pulmonary stenosis, and that coronary perfusion during the period of circulatory occlusion allows a longer period of safe intracardiac work.

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METHODS

The technique used with hypothermia and coronary perfusion has been changed little since our previous report. Pre-anesthetic medication includes promethazine (1 mg. per kilogram) the night before operation, and chlorpromazine (1 mg. per kilogram), meperidine (1 to 2 mg. per kilogram), and scopolamine (0.01 mg. per kilogram) the morning of operation. Pentothal and nitrous oxide are given for anesthesia with intermittent doses of succinylcholine to prevent shivering. The body temperature is lowered by surrounding the patient with chipped ice. The combined use of premedication, a muscle relaxant, and chipped ice has made possible lowering of the temperature of children in 5 to 15 minutes and adults in 20 to 30 minutes. Cooling is stopped at 32° to 33° C.; the temperature subsequently drifts to 30° to 31° C.

Ventilation is artificially maintained with oxygen and nitrous oxide and is slowed from a rate of 16 to 20 per minute at 37° C. to 10 to 14 per minute at 28° to 30° C. The pH of the arterial blood is measured at intervals and kept in the 7.40 to 7.60 range by varying the rate of ventilation. Alveolar carbon dioxide is no longer measured.

A right anterolateral thoracotomy through the fourth intercostal space is used for the repair of atrial septal defects, a bilateral thoracotomy through the right third and the left second intercostal space for patients with pulmonic valvular stenosis. During the period of venous occlusion for repair of the intracardiac defect, oxygenated, heparinized blood is perfused by gravity into the ascending aorta through a 1 cm. long, thin-walled, 18 gauge needle. The aorta is occluded distal to the site of insertion of the perfusion needle. Five hundred milliliters of blood in a standard transfusion bottle are suspended about 5 feet above the aorta, providing a perfusion pressure equivalent to 110 mm. Hg; a standard recipient set* connects the bottle to the perfusion needle. Blood will flow through the tubing and needle into an open syringe at 80 to 90 ml. per minute.

An important feature of the technique of repair of atrial septal defects is rotation of the patient to elevate the right side about 45 degrees. When the right atrium is opened, the left ventricle and atrium are thus lowermost and the septal defect is above them. Hence if blood is not aspirated from below the defect, the left ventricle will continue to pump blood returning to it from the lungs without danger of air embolism. Since the aorta is occluded distal to the perfusion needle, blood cannot escape from the heart and lungs. Difficulty has arisen from air entering the left ventricle in only two cases, one in which a ventricular septal defect apparently allowed emptying of the left ventricle into the right side of the heart and one in which the aorta was not completely occluded.

When a patient is positioned as described, some blood will flow from the coronary sinus to the right ventricle and be pumped through the lungs. This volume plus that in the lungs is sufficient to fill the left side of the heart, and in some instances a pressure above 110 mm. Hg is maintained in the occluded

*Fenwal Recipient Set, Fenwal Laboratories, Inc., Framingham, Mass.

aorta so that no perfusion occurs. In other patients little perfusion occurred until after 4 to 5 minutes of venous occlusion, by which time aspiration of blood had decreased the amount of blood returning from the lungs to the left ventricle. These observations suggest that, other than as a safety measure, especially when the pulmonary blood volume is large, coronary perfusion from the transfusion set is probably superfluous with periods of venous occlusion of less than 5 minutes but becomes of increasing importance with longer periods of occlusion.

RESULTS

Atrial Septal Defect.—Seventy-five patients with atrial septal defect have been operated upon with hypothermia and open cardiotomy (Table I). Twenty of these had associated anomalies of the pulmonary venous return, an incidence of 27 per cent; in 5 of the 20 patients a total anomaly of the pulmonary veins was present.[1] There were 7 deaths in the 75 patients, but only one death occurred in a child with an uncomplicated atrial septal defect, demonstrating the relatively low risk of the operation with present techniques. This death occurred early in the series and was associated with severe unexplained acidosis in a patient who had had two previous cardiac operations.[8] The other deaths resulted from technical difficulties with total anomalies of the pulmonary veins in two small children, pulmonary hypertension in one patient, an associated mitral insufficiency in 2 patients, and from ventricular fibrillation in a 38-year-old patient in whom coronary perfusion was inadvertently not used because of improper placement of the perfusion needle.

TABLE I. OPERATIONS FOR ATRIAL SEPTAL DEFECT

	NUMBER	PER CENT
Total patients	75	
Anomalous pulmonary veins	20	27
Deaths	7	9
Causes of death		
Total anomaly pulmonary veins	2	
Mitral insufficiency	2	
Pulmonary hypertension	1	
Fibrillation; no coronary perfusion	1	
Fibrillation; acidosis	1	

Coronary perfusion was used in 70 of the 75 patients. No perfusion occurred in 10; in this group the volume of blood recirculating through the heart and lungs was large enough to keep the aortic pressure above the pressure in the coronary perfusion system (110 mm. Hg). In some instances there was a reflux of blood from the aorta into the perfusion bottle.

The rate of coronary perfusion is shown in Table II. The total amount perfused was usually 50 to 200 ml.; the volume perfused exceeded 400 ml. in only 2 patients. This variation in the volume of blood added from the perfusion system seemed to depend on the volume of blood contained in the heart and lungs.

In the majority of patients venous occlusion was 6 to 7 minutes, but in 18 this time was greater than 8 minutes (Table III). No change in cardiac action was recognized with longer periods of occlusion.

TABLE II. RATE OF CORONARY PERFUSION DURING REPAIR OF INTRACARDIAC DEFECT

INTRACARDIAC DEFECT	NUMBER OF PATIENTS	RATE OF PERFUSION (ML./MIN.)					
		0	0-19	20-39	40-59	60-80	UNKNOWN
Atrial septal defect	70	10	18	27	10	3	2
Pulmonic valvular stenosis	13			6	6	1	0
Infundibular stenosis	3				1	1	1

TABLE III. DURATION OF VENOUS OCCLUSION DURING REPAIR OF INTRACARDIAC DEFECT

INTRACARDIAC DEFECT	NUMBER OF PATIENTS	DURATION OF OCCLUSION IN MINUTES			
		5 OR LESS	6-7	8-9	10-12
Atrial septal defect	75	13	44	11	7
Pulmonic valvular stenosis	20	14	5	1	
Infundibular stenosis	3		1	1	1

Pulmonic Valvular Stenosis.—Twenty patients with pulmonic valvular stenosis, 3 with infundibular stenosis, and 2 with combined valvular and infundibular stenosis have been operated upon employing hypothermia and coronary perfusion (Table IV). The one death in the 20 patients with stenosis of the valve was an unexplained one occurring suddenly 4 days after operation.[8] Two deaths in patients with combined valvular and infundibular stenosis resulted from intractable ventricular fibrillation in association with an uncorrected infundibular stenosis. The pulmonary valve ring was stenotic in both patients and could have been corrected only by the insertion of a patch across the pulmonary valve.

TABLE IV. OPERATIONS FOR PULMONIC STENOSIS IN 25 PATIENTS

INTRACARDIAC DEFECT	NUMBER OF PATIENTS	SURVIVORS	DEATHS
Pulmonic valvular stenosis	20	19	1
Infundibular stenosis	3	3	0
Combined valvular and infundibular stenosis	2	0	2

In the cases of valvular pulmonary stenosis, venous occlusion time was usually short (Table III) and there was less necessity for perfusion through the needle in the aorta (Table II). There was no recognized difference in behavior between the hearts which were perfused and those which were not. In the 3 cases of infundibular stenosis, venous occlusion lasted for 6 to 10 minutes and 55 to 75 ml. of blood per minute was perfused.

After operation, the pressure gradient between the right ventricle and pulmonary artery was less than 40 mm. in the 3 patients with infundibular stenosis and in 15 of the 20 patients with valvular stenosis. Five patients with valvular stenosis had large residual pressure gradients (72, 83, 95, 113, and 182 mm. Hg, respectively). This high residual gradient is presumably due to diffuse hypertrophy of the right ventricular muscle, for the fused valve

commissures were completely opened and a localized stenosis could not be palpated in the ventricle. Engle and associates[4] and Mahoney and associates[6] have reported spontaneous regression of this type of residual stenosis following valvulotomy.

Ventricular Fibrillation.—Ventricular fibrillation occurred in 12 of the 100 operations and was successfully treated in 7 (Table V). Defibrillation was unsuccessful in two patients with uncorrected infundibular stenosis. In three patients defibrillation was accomplished but death occurred several hours later.

TABLE V. VENTRICULAR FIBRILLATION DURING 100 OPERATIONS WITH HYPOTHERMIA

	NUMBER OF PATIENTS	VENTRICULAR FIBRILLATION	
		TOTAL	SURVIVORS
Intracardiac defect			
Atrial septal defect	75	8	5
Pulmonic valvular stenosis	20	1	1
Infundibular stenosis	3	1	1
Combined valvular and infundibular stenosis	2	2	0
Causes of Ventricular Fibrillation			
Myocardial irritability		7*	5
Absence of coronary perfusion		2	1
Air embolism		1	1
Acidosis		1	0
Pulmonary hypertension; air embolism		1	0
Total Cases	100	12	7

*Fibrillation from this cause occurred in 4 of 25 patients with pulmonic stenosis, 3 of 70 with atrial septal defect.

In 5 patients a condition was present which contributed to or caused the fibrillation. These included 6 minutes of venous occlusion without coronary perfusion in 2 patients, air embolism in one, pulmonary hypertension in one, and acidosis in one. The other 7 patients had no known cause for fibrillation other than increased susceptibility associated with hypothermia. None of the patients were acidotic; the temperature was in the 28° to 32° C. range. Fibrillation occurred in four during manipulation of the heart before venous occlusion was begun, in two during the period of venous occlusion, and in one shortly after termination of the venous occlusion.

Two of the 4 patients in whom fibrillation occurred during manipulation of the heart had an atrial septal defect; circulation was maintained by cardiac massage and defibrillation was accomplished after the body temperature had been raised from 28° to 30° C. by pouring warm saline on the heart. The other 2 patients whose hearts fibrillated from cardiac manipulation had pulmonic stenosis; one was treated by a closed transventricular valvulotomy and subsequent defibrillation, the other could not be defibrillated because of an uncorrectable stenosis of the pulmonic valve ring. Defibrillation was readily accomplished in 2 of the 3 patients in whom fibrillation occurred either during or after venous occlusion. The patient whose heart could not be defibrillated had infundibular stenosis.

Postoperative Course.—The postoperative course in most patients was a benign one. No instance of a bleeding tendency was recognized either during or following operation. None of the patients showed any circulatory collapse during the rewarming period or in subsequent hours. Three patients had a moderate acidosis after rewarming (pH values 7.19, 7.23, and 7.17, respectively), which readily responded to an intravenous infusion of sodium bicarbonate.

Most patients with atrial septal defect had a prompt decrease in heart size within a few weeks after operation in association with a decrease or disappearance of the systolic murmur which had been present before operation. Because of these clinical findings, postoperative catheterizations have not been done routinely. A recurrence of the defect has been suspected in one patient.

Three patients had some signs of neurological injury. Two of these were semicomatose for several hours after operation, following which their recovery was uneventful; one had circulatory interruption for 10 minutes at 32° C. and the other for 8 minutes at 33° C. The possible neurological injury might have been avoided in both patients if the temperature had been lower or the venous occlusion period shorter. The third patient, who had 8 minutes of circulatory interruption at 30° C., had intermittent convulsions for several days, with later complete recovery; unrecognized air embolism was considered a possible cause. Seven patients with circulatory interruption for 10 to 12 minutes at 28° to 30° C. had no signs of neurological injury.

Thrombosis of the superior vena cava and a bilateral chylothorax developed in one patient in whom the superior vena cava was partitioned to correct an associated anomalous venous return.[1] After several weeks of unsuccessful treatment with repeated thoracenteses, during which time the venous hypertension in the upper extremities subsided, the chylothorax was successfully treated by ligation of the thoracic duct.

DISCUSSION

In the 75 patients with atrial septal defect of the secundum type, without other complicating lesions except for anomalous pulmonary veins, only 2 deaths occurred. Coronary perfusion was inadvertently not used in one of these 2 patients, a 38-year-old patient with cardiac failure. The death from severe acidosis in the other patient would have been prevented by present methods. We believe coronary perfusion has been an important factor in this low risk and especially in increasing the time the venae cavae can be safely occluded. Swan, Kortz, Davies, and Blount[9] and Johnson, Kirby, Blakemore, and Zinsser[5] have recently reported a low mortality rate from patients operated upon without coronary perfusion. They clamp the aorta at the coronary arteries to prevent coronary flow and rigidly limit the venous occlusion time to 6 and 4 minutes, respectively. Coronary perfusion probably would not greatly affect survival if a limit of 6 minutes of occlusion were rigidly observed, but with coronary perfusion venous occlusion may be continued for 10 or 12 minutes if necessary, and one of the objections to hypothermia, that of necessary haste, may be partly dispelled. This additional time may be used

to visualize more clearly the defect and adjacent structures and to reinforce small leaks in the suture line. Multiple periods of occlusion are not needed. In this series of 75 patients, the duration of circulatory occlusion was 6 to 7 minutes in 44 patients and 8 to 12 in 18 (Table III).

A word of caution should be given in stressing essential features of this technique which are not immediately obvious or are different from that used by others.

1. A right anterolateral thoracotomy with the patient tilted to a 45 degree angle allows coronary sinus blood to flow into the tricuspid valve and the left atrium to remain full of blood so that the left ventricle may continue pumping. The supine position with a bilateral thoracotomy should not be used with this technique.

2. The aorta is clamped a convenient distance above the coronary arteries in order to have a small reservoir for coronary perfusion. *This is an essential difference from the technique which does not employ coronary perfusion, either autogenous or by transfusion.* Similarly no tourniquet is placed on the lung as left atrial and coronary flow are desired.

3. When the atrium is open, blood is aspirated from the right atrium only, never from below (or to the left of) the atrial septum. When this is done, blood usually spurts through small remaining holes as the defect is closed. Inflation of the lungs, which remain deflated during the circulatory occlusion, will force out additional blood to fill the left atrium and avoid trapping air as the closure is completed.

Patients with atrial defects more complicated than a simple secundum type should be operated upon with a pump-oxygenator. Such patients include those with an ostium primum defect, total anomaly of the pulmonary veins, pulmonary hypertension, or mitral valve lesions. All of these conditions can usually be diagnosed before operation. All but 2 of the 7 deaths in the atrial septal defect group were related to a defect in addition to that of the atrial septum.

Coronary perfusion did not seem necessary in the usual patient with pulmonic valvular stenosis, as circulatory occlusion was 5 minutes or less in most instances. Perfusion was of definite value, however, when an infundibular stenosis was found, as a longer time period was needed for ventriculotomy and excision of the stenosis. Since all 3 patients with infundibular stenosis were correctly diagnosed only after the pulmonary artery had been opened and the pulmonary valves found to be normal, it was fortunate that coronary perfusion had been used. Although the results in these three operations were satisfactory, we prefer at present to operate upon patients with a preoperative diagnosis of infundibular stenosis with cardiopulmonary bypass in order to have more time available for inspection and a wide excision of the stenotic area.

In the 25 operations for pulmonic stenosis 2 deaths resulted from narrowing of the pulmonary valve ring in addition to fusion of the valve leaflets. Correction of the narrowed ring would have required insertion of a patch, and sufficient time was not available with hypothermia to accomplish this. Because

of inadequacy of the technique in 2 cases from a total of 25, we anticipate more frequent use of cardiopulmonary bypass for pulmonic stenosis with an intact ventricular septum, a policy already adopted by McGoon and Kirklin.[7]

The two most serious potential complications associated with the use of hypothermia and coronary perfusion are ventricular fibrillation and neurological injury. Seven of the 12 instances of ventricular fibrillation that occurred in 100 operations were without known cause other than increased susceptibility to fibrillation associated with hypothermia. The likelihood that this explanation is the correct one is supported by the fact that 4 of the 7 instances occurred with manipulation of the heart before circulatory occlusion was begun. Fortunately, fibrillation that occurs in these circumstances can usually be readily corrected by massage and electrical defibrillation.

We have not recognized a specific neurological injury in any patient as a result of prolonged venous occlusion. Circulatory interruption at 30° C. for longer than 12 minutes is probably unwise because of the danger of cerebral injury, although the data needed to define this limit are not available. A period of coma lasting several hours in 2 patients in this series may have resulted from cerebral ischemia, although the patients subsequently showed no ill effects, and other causes of central nervous system injury could not be excluded. Their periods of circulatory occlusion were 10 minutes at 32° C. and 8 minutes at 33° C.

SUMMARY

One hundred patients are reported who had intracardiac defects corrected during temporary circulatory occlusion under hypothermia. Coronary perfusion with oxygenated blood during the period of circulatory occlusion was used in most patients. There were 75 patients with an atrial septal defect (20 of whom had associated anomalies of the pulmonary veins), and 25 with pulmonic stenosis, either valvular or infundibular.

Coronary perfusion was used in 70 of the 75 patients with atrial septal defect. The rate of perfusion varied from 20 to 60 ml. per minute in most patients. The duration of venous occlusion was 6 to 7 minutes in 44 patients and 8 to 12 minutes in 18 patients. Seven deaths occurred in the entire group, but only 2 occurred in patients with an uncomplicated atrial septal defect. Coronary perfusion was valuable in lowering the operative risk and in increasing safely the time the venae cavae could be occluded. This conclusion is supported by the low incidence of ventricular fibrillation with periods of occlusion as long as 12 minutes.

Coronary perfusion was used in 13 of the 20 patients with pulmonic valvular stenosis and in all 3 patients with infundibular stenosis. As the circulation was interrupted for less than 5 minutes in most of the patients with valvular stenosis, coronary perfusion did not seem of significant value. It was of value, however, in the 3 patients with infundibular stenosis in whom a longer period of circulatory occlusion was necessary.

These experiences have led to the conclusion that the combination of hypothermia and coronary perfusion is a simple, safe, and effective method in the

treatment of uncomplicated atrial septal defect and of pulmonic valvular stenosis. Precautions in the use of this method have been given. A pump-oxygenator should be used if the intracardiac defect is a more complicated one.

REFERENCES

1. Bahnson, H. T., Spencer, F. C., and Neill, C. A.: Surgical Treatment of 35 Cases of Drainage of Pulmonary Veins to the Right Side of the Heart, J. Thoracic Surg. 36: 777-802, 1958.
2. Bigelow, W. G.: Hypothermia, SURGERY 43: 683-687, 1958.
3. Brockman, S. K., and Fonkalsrud, E. W.: Experimental Open Heart Surgery Employing Hypothermia, Mecholyl Arrest, and Carotid Perfusion, SURGERY 43: 815-823, 1958.
4. Engle, M. A., Holswade, G. R., Goldberg, H. P., Lukas, D. S., and Glenn, F.: Regression After Open Valvotomy of Infundibular Stenosis Accompanying Severe Valvular Pulmonic Stenosis, Circulation 5: 862-873, 1958.
5. Johnson, J., Kirby, C. K., Blakemore, W. S., and Zinsser, H. F.: Intermittent Inflow Occlusion for the Direct Visual Repair of Atrial Septal Defects, J. Thoracic Surg. 37: 314-319, 1959.
6. Mahoney, E. B., Manning, K. A., DeWeese, J. A., and Schwartz, S. I.: Clinical Results of Correction Under Hypothermia of Atrial Septal Defects and Pulmonary Valvular Stenosis, J. Thoracic Surg. In press.
7. McGoon, D. C., and Kirklin, J. W.: Pulmonic Stenosis With Intact Ventricular Septum, Circulation 17: 180-186, 1958.
8. Spencer, F. C., Jude, J. R., and Bahnson, H. T.: The Use of Coronary Perfusion and Carbon Dioxide Regulation in Intracardiac Operations Performed Under Hypothermia, SURGERY 42: 76-91, 1957.
9. Swan, H., Kortz, A. B., Davies, D. H., and Blount, S. G.: Atrial Septal Defect, Secundum, J. Thoracic Surg. 37: 52-80, 1959.

Appraisal of Progress in Surgical Therapy

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A CRITICAL REVIEW OF THE TREATMENT OF MAMMARY CARCINOMA

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FOR many surgeons the treatment of carcinoma of the breast is in a confused state. Conflicting opinions are found in the literature. Certain simple procedures have been advocated which have encouraged improperly trained physicians to undertake the care of patients with this disease. As a result, many women are paying with their wealth and with their lives for inadequate therapy. The initial cause for the present confusion can be traced to the publications of McWhirter,[7] in which he has questioned the superiority of the classical Halsted operation over simple mastectomy combined with irradiation therapy. Other factors adding to the complexity of the problem have been the introduction of superradical operations and the advent of hormonal therapy. In addition, there is the unreliability of statistical studies by physicians. This is particularly true when the subject is as complex as treatment of carcinoma of the breast. There are several reasons why this is so. First, there are only a few clinics in the world where a sustained and critical study of diseases of the breast has been pursued. These clinics alone are able to provide reliable data. Second, there are wide variations in the operations which are designated as radical mastectomies; many are radical in name only. Consequently the results attributed to the operation are misleading. Third, the astuteness and thoroughness of the pathologists who examine the specimens differ as widely as the hospitals in which they work. Finally, carcinoma of the breast is not a clinical entity, but is actually a family of malignancies in which each member may behave in an unpredictable manner, and, although identical histologically, one tumor may be fatal in a few months, while its twin may live symbiotically with the host for a long time. The functional history of the organ bearing the tumor runs the gamut from breasts which have never lactated to those in which there have been frequent and prolonged periods of lactation. The patients also differ as to inheritance, age, nutrition, endocrine balance, and previous illnesses. Any of these many variables may alter the course of the neoplasm. Some cannot be determined, and the others are often not considered when therapeutic results are reported. Unfortunately, therefore, most of the statistical studies and some of the books on carcinoma of the breast are quite worthless.

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For every patient at any particular phase of the disease there is a course of treatment which is best. One must therefore study each patient and weigh all the factors pertinent to treatment. Realizing that it is impossible to cure more than a limited number of women with malignant tumors of the breast, one must have a clearly defined objective, such as to give every patient every possible assistance toward comfortable survival. This means, when a cure is possible, that the patient should have a radical mastectomy, expertly performed as promptly as possible. It means also that in all other cases the patient must be given sustained assistance with combinations of surgery, irradiation, hormones, chemotherapy, and symptomatic medication. In other words, a surgeon has just as great an obligation to care for the woman whose tumor is incurable as for the one whose carcinoma can be totally eradicated. This does not mean that it is his duty to prolong mere existence as long as possible, but rather in the hopeless stages of the disease to direct all his efforts toward keeping the patient comfortable. With the objective in mind, the therapeutic methods of reaching it can now be appraised. For the sake of clarity the subject will be dealt with under two headings: first, the management of patients in whom there is reasonable expectation of a complete cure; and, second, the management of those for whom this is not true.

CURABLE MAMMARY CARCINOMA

What constitutes the grounds for a reasonable expectation of a complete cure? These conditions have been stated by Haagensen[5] and Purdy Stout who, through their sustained and careful studies, not only clearly defined operability for carcinoma of the breast, but also have emphasized the basic fact that at present the only means of eradicating a carcinoma of the breast is by surgery. Haagensen's biopsy criteria of inoperability are: (1) Extensive edema of the skin over the breast (more than one-third of the skin area); (2) satellite nodules in the skin over the breast; (3) inflammatory type carcinoma; (4) any two, or more, of the following grave signs of locally advanced carcinoma: (a) ulceration of the skin, (b) edema of the skin of limited extent (less than one-third of the skin over the breast), (c) solid fixation of the tumor to the chest wall, (d) axillary lymph nodes measuring 2.5 cm. or more in transverse diameter, (e) fixation of axillary lymph nodes to the skin or the deep structures of the axilla; (5) edema of the arm; (6) palpable supraclavicular nodes and biopsy showing metastases; (7) biopsy of the internal mammary nodes in the first, second, or third intercostal spaces, and/or at the apex of the axilla revealing metastases; and (8) distant metastases.

There are many patients who cannot afford the time or the expense of two operations, and in these cases the surgeon must rely upon the preceding criteria of operability without the benefit of biopsy data. It is generally conceded that, when these criteria are met, the patient has a reasonable expectation of a cure, provided a thorough Halsted mastectomy is performed. It is not possible to give a detailed description of the ideal radical mastectomy. The enquiring surgeon, however, can find this done with exquisite precision by Haagensen[5]

in his book, *Diseases of the Breast.* He has drawn a sharp distinction between the "standard American radical mastectomy" and the Halsted operation. Although an account like his cannot be duplicated here, it is important to describe unambiguously just what is denoted by the term *radical mastectomy* as used in this communication.

Before starting an operation for carcinoma of the breast, the surgeon should remember that he is about to begin a task which gives the patient her one and only chance for a cure. When she leaves the operating table she will or will not be totally free of carcinoma. It is imperative that a donor site for a skin graft be made when the operating fields are being prepared. The anticipation of grafting in every case is the surest guarantee that the surgeon will be unrestrained when he outlines the incision he is about to make. If a biopsy has been performed (and an excisional biopsy with the cautery is always preferable to an incisional one) all drapes, gowns, gloves, and instruments must be changed. Nearly all of the skin of the breast should be removed. The skin flaps should be exceedingly thin. The dissection should be carried out between the most superficial layer of the fascia and the corium. To facilitate doing this, the flaps should be kept on tension. The boundaries for the lateral flaps should be the costal margin, the edge of the latissimus, and the clavicle. The insertion of the pectoralis major should be cut close to the humerus so that the axillary dissection can be started laterally and carried medially. To gain access to the highest part of the axilla, it is necessary to divide the pectoralis minor at its attachment to the coracoid process. There is often a temptation with obese patients to remove some of the axillary fat by blunt dissection, but this merely disseminates carcinoma cells throughout the wound. After the minor muscle is cut at its origin and some of the rectus fascia is excised, the breast is reflected medially to expose the perforating vessels entering the undersurface of the major muscle. These vessels, with the accompanying lymphatics, are clamped and divided before the pectoralis major is cut from the sternum. The thin medial skin flap is then dissected to the sternum in an avascular field. The closure of the wound is carried out by suturing the skin flaps to the chest wall under normal tension. In most cases the flaps do not meet and the resultant defect is covered with a graft. The insertion through a stab wound of two small rubber catheters with multiple openings provides a means of suction (30 inches of water) during the first and second postoperative days, and this plus gentle pressure from the dressing ensures a dry wound.

The electrocautery is used only for biopsy and to coagulate vessels in the tissues which are to be removed. Fine silk is used throughout for ligatures and sutures. The wound is frequently irrigated with nitrogen mustard or Dakin's solution. Cole[3] has shown in experimentally inoculated wounds the value of these solutions in killing malignant cells and the inability of saline, distilled water, and other solutions to do so.

One cannot overemphasize the importance of gentleness in the handling of the breast containing a malignant growth or the importance of a wide excision, en masse, of skin, breast muscles, and axillary tissues. There are two reasons

for the poor results following operations for carcinoma of the breast. The first is the poor selection of cases, but the most serious reason is the substitution of subradical operations for a genuine Halsted procedure. Some of the reasons for this whittling down are: first, laziness on the part of surgeons, many of whom find meticulous dissection irksome; second, the allocation of insufficient time for the operation; and third, inadequate training, hence unfamiliarity with the principles of a radical procedure. It is a lamentable fact that more than half of the patients with carcinoma of the breast in the United States are operated upon by general practitioners, osteopaths, and incompetent operators who are unable to meet the training requirements of the American Board of Surgery or the American College of Surgeons. This statement is based on factual data presented to the American Surgical Association.

In addition to a radical mastectomy there are two ancillary procedures which are of probable but, as yet, unproved value—the systemic administration of nitrogen mustard[3] at the time of operation, and the giving of testosterone for a period of 3 or 4 weeks postoperatively, which is insufficient to produce virilizing effects and yet may perchance inhibit the growth of freshly implanted malignant cells. The use of postoperative irradiation in patients who have had a radical mastectomy is indicated only when the tumor is in the medial part of the breast. In these cases, therapy over the ipsilateral parasternal nodes is desirable.

In summary, one cannot state too strongly that at present the only treatment for mammary carcinoma when there is a reasonable expectation of cure is a thorough radical mastectomy. Only in patients too frail to withstand such a procedure is a limited operation permissible.

INCURABLE MAMMARY CARCINOMA

We now come to consideration of those patients whose disease is more extensive. This group comprises patients with all degrees of advanced disease. There are those with such extreme local extension or with remote metastases for whom no attempts are made to treat the tumor. One's efforts are directed entirely toward ministering to the patient's comfort in these cases. There are others in whom some benefit to the patient may be expected by treating the tumor. It is in this latter group that the greatest differences of opinion occur. For these patients there are at least four possible courses of therapy: irradiation, surgery and irradiation, superradical surgery, and hormones.

Irradiation.—The rate of discovery in the physical sciences has been so rapid and the effects of physical energies on living cells are so uncertain that a final appraisal of the role of irradiation therapy is impossible. Definitive judgment is further delayed when one realizes that there are relatively few qualified radiotherapists in the United States. The American Board of Radiology certifies its diplomates as "radiologists," which implies adequate training in both the diagnostic and the therapeutic aspects of the subject. Actually the requirement for qualification is a minimum of 6 months' training in therapy. It is much easier for an institution to acquire cobalt^{60} and equipment than it is

to secure a doctor who is experienced in its use. Consequently, the practical problem in prescribing radiotherapy turns out to be a geographic one, or in other words the accessibility of a competent radiotherapeutist. It is unrealistic to expect to obtain the same results in the average American hospital that are secured in the large radiologic institutes. There is an additional factor of prime importance that must be emphasized before considering irradiation of mammary carcinoma. Even with the highest dosage the tumor is seldom totally eradicated. Studies such as those by Baclesse,[2] who used 4,500 to 9,000 r. and then after sufficient time removed the breast for histologic examination, have shown that over 88 per cent still had apparently viable malignant cells. The clinical records at the Presbyterian Medical Center have shown that tumors after heavy irradiation are suppressed but eventually recur and prove lethal. However, one must emphasize, as Russ[9] points out, that an adequate interval may not have elapsed for an evaluation of the very high voltage technique. The advent of cobalt^{60} and caesium^{137} which emit gamma rays as well as beta may revolutionize the technique of radiotherapy, and consequently enhance its efficacy to the point where the results are superior to those following ablative surgery.

As emphasized previously, the use of radiotherapy as the sole means of treatment for mammary carcinoma is permissible only in those instances in which the tumor is too advanced to be treated surgically. When it is used, an all-out effort must be made by the radiologist. Too often a trifling amount of x-ray is given as a placebo to the patient. It is doubtful if any good is derived from such deception. Occasionally, a tumor is so sensitive that an inoperable lesion becomes operable. When this happens the complete radical mastectomy is indicated. Recent studies indicate that a minimum of 4,500 r. should be given tangentially through the breast. The side effects of fractional x-ray emanating from a 2,000 kilovolt machine are less than those from the ordinary 250 kilovolt apparatus. For the present it seems wise that, when the only treatment to be given is irradiation, the patient should be sent to a radiologic institute or to a university center. An excellent presentation of the whole subject of irradiation therapy has just been made by Murphy[8] of the Roswell Park Memorial Hospital.

Preoperative irradiation was abandoned some 20 years ago following critical studies by Greenough and others, but recently there has been a revival of this adjuvant therapy for patients whose tumor is classified as advanced Stage II or Stage III. The impression of the staff at the M. D. Anderson Hospital in Houston is that irradiation of such carcinomas followed in 6 weeks by a thorough radical mastectomy gives better results than operation alone.

Surgery and Irradiation.—The second possibility in handling patients with advanced carcinoma of the breast is a combination of irradiation and surgery. If a patient follows the tenets of Haagensen, he would never operate upon any of these patients. If, on the other hand, a surgeon's aim is to give every patient every possible assistance toward the maximum comfortable survival, then there are some women on whom he will use both surgery and irradiation.

A plausible argument for either position can be made. One has to weigh the psychic distress and the physical handicap of a radical mastectomy against the satisfaction and actual benefit of having the primary growth removed. Most women prefer to have the breast removed than to be constantly aware of the presence of a malignant tumor. Furthermore, it is probable that the removal of the primary source of metastases reduces greatly the dissemination of additional ones. It is reasonable to think that the irrigation of the wound with nitrogen mustard or Dakin's solution during the operation may eliminate the hazard of spreading the tumor when the surgeon cuts across carcinomatous tissues. It has been shown that metastatic lesions behave differently than primary growths. Most surgeons have seen metastases respond to hormones, whereas the primary tumor did not, and vice versa. For these reasons a fair case can be made for performing the Halsted operation even though the likelihood of a cure is not great. There is an additional factor that must be considered, and this is the economic status of the patient. There are hundreds of poor working folk who cannot afford the time or the expense necessary for adequate radiation therapy. These women, however, can be helped by a radical mastectomy plus hormone therapy.

An alternative combination of surgery and irradiation is that advocated by McWhirter,[7] namely, a restricted or simple mastectomy followed in 2 weeks by intensive irradiation. His main contention has been that surgery is effective only when the carcinoma can be completely extirpated, and that once the axillary nodes contain metastases the disease in all but a few cases has already spread beyond the reach of surgery. He has also maintained that axillary dissection disseminated the neoplasm and that irradiation is more effective against carcinomatous nodes than it is against the primary lesion. These assumptions, however, have been refuted by certain facts. Handley[6] has shown that only 28 per cent of internal mammary nodes were positive when the tumor was in the lateral half of the breast and the axillary nodes contained metastases. The contention that the axillary dissection disseminates the tumor certainly ignores the fact that a simple mastectomy of a carcinomatous breast inevitably does so to a greater degree. His third statement about the relative susceptibility of axillary metastases to irradiation is contrary to experience and fact. Ackerman[1] examined axillary nodes which had been removed from McWhirter's patients after a full course of therapy by him, and in every instance found malignant cells apparently unaltered. McWhirter's oft-quoted results are misleading because 220 of the 719 patients had concomitant sterilization, and in all patients with persistent lesions additional therapy with hormones was given. Furthermore, according to Ackerman, 14 of the patients did not have carcinoma to begin with, and some had had radical mastectomies. Obviously, therefore, McWhirter's figures do not permit a critical comparison of his method with others. As Ackerman[1] has stated, the figures from Edinburgh represent mere survival and "if we take McWhirter's figures for 5 year survival and subtract the number of patients with local or distant evidence of disease then his cure rate

is rather low.'' It must be emphasized too, as Dr. Barney Brooks concluded after a personal study, that the operations which gave cause for McWhirter's dissatisfaction were not true Halsted mastectomies, but very restricted modifications.

The objections to McWhirter's management of carcinoma of the breast are four: First, many patients with curable lesions have been subjected to inadequate surgery and hence have died unnecessary deaths. Second, the incidence of skin metastases after his treatment is much greater than when a Halsted operation with graft is performed. Third, the postradiation morbidity is greater than that following surgery. Fourth, without the knowledge gained from an axillary dissection one is not able to differentiate between a Stage I and a Stage II lesion and hence is treating the patient blindly. There is, moreover, the practical problem that the time required and the expense of thorough irradiation are more than most patients can afford.

One must pause here to point out the great damage resulting from McWhirter's teaching. His publications, with the prestige of the Edinburgh Infirmary behind them, have served as justification to hundreds of general practitioners and other untrained operators to employ simple mastectomies in patients who could have been cured if a radical procedure had been carried out. Not only have these operators done partial mastectomies, but usually the subsequent radiation therapy has been given by men with insufficient training and with antiquated equipment. This combination has cost many women their lives.

It seems clear that simple mastectomy with irradiation should be reserved for those few patients who are either too frail, too old, or too sick with concomitant disease to withstand extensive surgery. It is nothing short of criminal to use McWhirter's method routinely, for it denies patients with curable disease their one chance of cure. For most patients with incurable disease a radical mastectomy plus irradiation of the parasternal nodes offers the least morbidity and the longest life expectancy.

Superradical Surgery.—Dissatisfaction with results with the conventional modes of treatment has spurred surgeons to try superradical operations. Richard Handley,[6] in England, has described a procedure in which a block of the chest wall, including the second, third, and fourth costal cartilages, the intercostal muscles, and the intermammary vascular bundle with nodes is excised after the breast, pectoralis minor, and axillary tissues have been removed. He closes the defect in the chest wall with the pectoralis major muscle. He reported with Patey that only 40 per cent of the patients subjected to this extensive operation were found to have metastases in the internal mammary nodes.

For 10 years Dahl-Iverson,[4] in Copenhagen, has been using a more conservative method of extrapleural removal of the internal mammary chain, and has combined this with a radical mastectomy and supraclavicular dissection of nodes. Urban,[10] in New York, has reported a series of 160 patients in whom he combined a radical mastectomy with en bloc removal of a portion of the sternum and chest wall in the parasternal region. The defect was closed with

fascia lata. In 40 per cent of these patients no involvement of axillary or internal mammary nodes was found. Other extensions of these procedures have been carried out, culminating in Prudente's ultraradical mastectomy combined with interscapular-thoracic amputation.

The final appraisal of these extended operations which remove the internal mammary chain must await convincing data showing a cure rate sufficiently high to offset the additional morbidity. This will probably never be forthcoming because when these nodes contain metastases the likelihood is exceedingly great that the disease has already spread beyond them. It must be stated that many lives will be needlessly shortened if any but the most experienced surgeons attempt these superradical procedures.

Hormones.—If our knowledge of the physiology of internal secretions were complete, we could probably use them with precision to block the growth of malignant tumors of the ovaries, breast, and prostate. Indeed, it is possible that one could prevent the occurrence of malignancy in these organs. For the present, hormone therapy for carcinoma of the breast is merely an adjuvant which is sometimes used with surgery and irradiation, but more frequently it is resorted to when these have failed. Paradoxically, both the deletion of estrogen and the administration of it are sometimes helpful in the treatment of this disease. The deletion, or rather diminution, of estrogen formation in the body has been attempted off and on since 1896 when bilateral oophorectomy was first done by Beatson. From time to time conflicting reports have appeared concerning the effect of this operation on the course of mammary carcinoma, and even today convincing data are lacking to prove its value. It seems clear that suppression of estrogen formation by irradiation of the ovaries is seldom complete, and hence surgical removal is preferable if castration is desired. At present there is not sufficient evidence to justify oophorectomy as a routine procedure in premenopausal women in the hope that this will prevent a recurrence of the malignancy. There are, however, instances of soft tissue metastases where this operation has been used effectively to retard the growth. Theoretically a bilateral adrenalectomy should be done at the same time since these glands also form estrogen. In 1951 a study by a committee of the American Medical Association's Council of Pharmacy and Chemistry indicated that the giving of various estrogens to postmenopausal women brought about regression of soft tissue metastases in about one-half of the patients. There was no preference as to which estrogen was used. There is general agreement that the older the patient, the better the effect, and that it is unwise to give estrogen to premenopausal patients.

The use of androgens, prophylactically after a radical mastectomy, has been referred to. The administration of androgens to women for the alleviation of pain from osseous metastases is a generally accepted treatment. The usual dosage is from 20 to 40 mg. of testosterone propionate daily for 3 months. This can be given by tablets for buccal absorption, or intramuscularly. When given along with calcium gluconate, one can occasionally observe the union of a

pathologic fracture or the calcification of an osseous metastasis. In premenopausal women androgen therapy is indicated for soft tissue recurrences of the tumor. In men with carcinoma of the breast the elimination of androgen by castration gives consistently good results.

The puzzling and distressing fact about all hormonal therapy for malignant disease is that the results are unpredictable and never permanent. What is needed is more accurate knowledge about these substances, and, in particular, means of augmenting their potency, eliminating undesirable side effects, and lengthening the duration of their beneficial action. The most recent efforts to stem the progress of metastatic disease have been the extirpation of the adrenals, and either the removal or destruction of the hypophysis. In a few of Huggin's patients with bilateral adrenalectomy, the regression of the tumor has been astounding. The same can be said for some of the effects following hypophysectomy. The magnitude of these procedures is so great that they are used only when all other forms of therapy have failed. For the time being they must be looked upon as experimental exercises.

REFERENCES

1. Ackerman, L. V.: Evaluation of Treatment of Cancer of Breast at University of Edinburgh (Scotland), Under Direction of Dr. Robert McWhirter, Cancer **8**: 883-887, 1955.
2. Baclesse, F.: Method of Pre-operative Roentgentherapy by High Doses Followed by Radical Operation for Carcinoma of Breast (Showing Survivals up to 10 Years) (Skinner Lecture), J. Fac. Radiologists **6**: 145-163, 1955; correction 6: 233, 1955.
3. Cole, W., Mrazek, A., Economou, S., McDonald, G. V., and Slaughter, D.: Prophylactic and Adjuvant Use of Nitrogen Mustard in the Surgical Treatment of Cancer, Tr. Am. Surg. A., 1959.
4. Dahl-Iverson, E.: Carcinoma of the Breast, Official Tr. Northern Surg. A., Copenhagen, 1951.
5. Haagensen, C. D.: Diseases of the Breast, Philadelphia, 1956, W. B. Saunders Co.
6. Handley, R. S., Patey, D. H., and Hand, B. H.: Excision of the Internal Mammary Chain in Radical Mastectomy, Lancet **1**: 147, 1956.
7. McWhirter, R.: Simple Mastectomy and Radiotherapy in Treatment of Breast Cancer, Brit. J. Radiol. **28**: 128-139, 1955.
8. Murphy, Walter T.: Radiation Therapy, Philadelphia, 1959, W. B. Saunders Co.
9. Russ, J.: Cancer, edited by Raven, Vol. V, London, 1959, Butterworth & Co., Ltd.
10. Urban, J. A.: Extension of Radical Mastectomy to Include Mammary Lymph Node Chain, West. J. Surg. **63**: 463-469, 1955.